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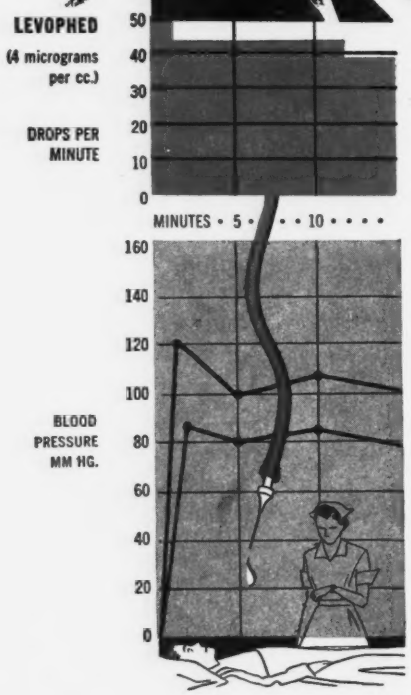

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The George E. Brown Memorial Lecture

Some Chemical Factors in the Pathogenesis of Atherosclerosis

By DAVID P. BARR, M.D.

STATISTICS indicate that half of those who die at the age of 50 and more than 85 per cent of those who die after 75 are afflicted with moderate or advanced atherosclerosis.[1] The disease is not dependent upon the circumstances of modern life.[2, 3] Although its extent and complications may vary considerably with race,[4-6] sex,[7] age,[1] family[8, 9] profession,[10] the state of nutrition,[1, 11] and a variety of pathologic states, some tendency to its development is apparent in most human adults. One must infer that conditions otherwise regarded as normal permit the formation of atheromatous patches in blood vessels.

Man appears to be unique among mammals in his predisposition. Dogs, cats, rabbits, rats, guinea pigs, higher anthropoids and other wild mammals seldom, if ever, develop spontaneous atherosclerosis.[12, 13] It would seem that in the constitution of man, there is some anatomic or chemical peculiarity that makes him especially susceptible to the deposit of abnormal lipids in the walls of large and medium sized arteries.

The influence of anatomic factors in the pathogenesis of atherosclerosis cannot be denied. It is attested by the patchiness of lesions, by their selective localization in areas of intimal thickening[14] and by the evidence that damage to the circulation in the arterial wall fosters deposit of lipids at the site of injury.[15, 16] The patches develop, however, and may become widespread in arteries which reveal no traces of previous structural deviation. Although species differences in the adequacy of circulation in the arterial wall might be suspected as a factor, there is no understandable correlation between vascularity and predisposition to atherosclerosis.[17] Indeed, no significant anatomic differences between the arteries of man and other mammals have as yet been established.

Attention may therefore be focused on the possibility that something in the chemical constitution of man makes him more vulnerable. The following discussion will be concerned with three main questions:

1. Does the lipid composition of plasma in man differ from that of mammals which are not susceptible to spontaneous atherosclerosis?
2. Are variations in human predisposition signalized by differences in the lipid composition of plasma?
3. Is it possible that presumably undesirable characteristics of the chemical composition of human plasma could be modified by therapeutic agents?

METHODS OF STUDY OF THE LIPID COMPOSITION OF PLASMA

The methods by which these problems may be attacked are limited. Since there are at present no adequate procedures for the in-

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vestigation of the state of lipids in tissues and since study of the composition of lymph has only begun,[18, 19] chemical information is derived almost entirely from examination of plasma or serum.

Earlier investigations were confined to the analysis of separate lipid constituents (cholesterol, phospholipids, fatty acids and neutral fats) and to their relation to each other in plasma. While any or all of the interrelationships might be of possible significance, particular attention was and is still given to the ratio of cholesterol to phospholipids. Later it was found that the examination of individual lipids could afford only partial information.

It has been known for some time[20] that cholesterol and phospholipids do not circulate in the plasma in molecular solution, but on the contrary, are combined with each other and with proteins as compounds or aggregates which are known as lipoproteins. In the past few years, these have received extensive scrutiny by many observers and by a variety of methods. In the laboratory at Cornell[21] we have utilized Cohn's microfractionation method number 10.[22] Gofman[23, 24] and others[25] have been occupied with the information to be gained from ultracentrifugation of serum.

From the combined experience of many investigators it now appears that in normal human plasma and in plasma of many pathologic conditions essentially all of the cholesterol and phospholipid of plasma or serum is combined with one or the other of two groups of proteins, with $alpha_1$ globulins as alpha lipoproteins or with $beta_1$ globulins as beta lipoproteins. Although knowledge of these substances is as yet extremely fragmentary, it has been determined that the two types of protein differ from each other not only in their molecular weights and many other physical characteristics, but usually also in their capacity to combine with various lipids of the plasma. Perhaps the most significant difference from the standpoint of subsequent discussion is in the cholesterol–phospholipid ratios of the two groups. The alpha lipoproteins are found to have cholesterol–phospholipid ratios by weight of about 0.50 while the beta lipoproteins, as indicated by samples purified from pooled, presumably normal human plasma, have a ratio by weight of over 1.00.[26] Evidence is accumulating from many sources, however, that each group of lipoproteins is made up of a number of individual compounds or aggregates in which the protein moiety is combined with variable amounts of lipids.

The S_f 10–20 bodies which were the original focus of the ultracentrifugal studies of Gofman and his associates have not been precisely identified. The question whether they form a small part of the total beta lipoproteins is as yet unsettled.

In the differential ethanol separation of Cohn's microfractionation method number 10 the two types of lipoproteins are usually concentrated in separate fractions. Cholesterol–phospholipid ratios and electrophoretic determinations of the fractions from plasma in normal individuals[21] and in atherosclerotics and conditions that predispose to its development[27] have indicated that the separation of lipid-bearing proteins is reasonably complete and that the lipids recovered from fraction IV + V + VI are in combination with $alpha_1$ globulin and that those found in fraction I + III are combined with $beta_1$ globulin. To assume that this is completely or always true disregards the possibility of systematic or occasional contamination of each fraction by the proteins of the other and also fails to consider the contingency that in the individual plasma, unusual lipid-bearing proteins may be present. That lipoproteins of abnormal lipid and protein composition may exist in at least one condition, namely that of biliary cirrhosis, has been indicated by our own studies of the cholesterol–phospholipid ratios and by the recent investigations of Kunkel and Slater[28] with the method of zone electrophoresis. Certainly the possibility of abnormal lipoproteins must be considered in the study of animals or of any condition which represents a modification of the normal human state either by manipulation or by disease.

Nevertheless in our previous publications[21, 29, 30] and in the discussions and tabulations which follow, the cholesterol and other lipids recovered in fractions IV + V + VI are represented as forming a part of alpha lipo-

proteins and those found in fractions I + III as a part of beta lipoproteins. It is important to emphasize that this has been done for the sake of convenience in presentation and reference, but with the realization that establishment of the assumption in general will require much further investigation.

Relation of Lipid Constituents of Plasma to Atherosclerosis

As a consequence of the chemical studies, several ideas have been advanced concerning the relation of the lipid constitution of plasma to the pathogenesis of atherosclerosis.

1. In the past, much emphasis has been placed on the possibility that the deposit of atheromatous material in the arterial walls may be dependent simply upon the concentration of total cholesterol in the plasma.[31, 32]

2. Others[33-36] have advanced the idea that it is not the cholesterol level alone that is significant, but that the development of atherosclerosis may depend upon the ratio of cholesterol to phospholipid in plasma.

3. The trend of our own investigations has led us to place emphasis upon the possible pathogenetic significance of the distribution of lipids between the alpha and beta lipoproteins.[30]

4. Gofman and his associates have been intrigued with the possibility that the presence and concentration of specific substances such as S_f 10–20 bodies are of crucial significance in the development of atherosclerosis.[23]

In the first part of the discussion which follows, an attempt will be made to keep all of these hypotheses in mind, to show possible relationships of each to the others under a variety of special circumstances, and to offer some hints as to the probable relative significance of the data revealed by the different methods.

Lipid Composition of Human Plasma

In table 1, *approximate* values of the various constituents and relationships in normal adult human plasma have been assembled for the purpose of comparison with those of other mammalian species. The figures for cholesterol, phospholipid and cholesterol–phospholipid ratios approximate results obtained in young normal adults by Gertler, Garn and Lerman[36] and by Russ, Eder and Barr.[21] The values for the distribution of cholesterol between the two groups of lipoproteins as well as the cholesterol–phospholipid ratios of the alpha and beta lipoproteins are approximate averages of data from our laboratory on young men and women. The values for S_f 10–20 are indicative of the averages for young normal males submitted by Gofman and his associates in their report in Circulation in 1950.[23]

Table 1.—*Lipid Composition of Human Plasma. Approximate Values Assembled from Several Sources but Not Reflecting Precisely Any Published Data.*

Total cholesterol (mg. %)	200
Phospholipids (mg. %)	250
Chol./PL. ratio	
Plasma	0.80
Alpha lipoprotein	0.50
Beta lipoprotein	1.25
% total cholesterol in alpha lipoprotein	30
% total cholesterol in beta lipoprotein	70
S_f 10–20 (mg. %)	12

Comparison of Lipid Values in Man and other Mammals

Studies of lipids in mammals other than man that involve all of the criteria of the present discussion have not been undertaken in any single laboratory. Data from several sources permit a partial comparison of man with the rat and a reasonably complete comparison of man with the dog and the rabbit. The available information has been assembled in table 2.

The values for cholesterol, phospholipids and cholesterol–phospholipid ratios in the dog, rabbit and rat are taken from unpublished data of Dr. Forrest E. Kendall and are included by his very kind permission.[37] The figures for the distribution of cholesterol between the alpha and beta lipoproteins as well as the cholesterol–phospholipid ratios of the two fractions are our own.[21] The information concerning S_f 10–20 bodies is taken from the publications of Gofman[23] and of Lewis, Green and Page.[25]

It will be seen that the averages for total cholesterol are almost identical in man and

dog. Kendall's range of values for the dog is not given in the table, but does not deviate significantly from that of the normal human adult.[36] In passing, it is worthy of note that if the concentration of cholesterol were to be regarded as the only criterion, no difference in predisposition to atherosclerosis in dog and man would be anticipated.

The phospholipid values on the contrary are much higher in dogs than in man, 430 mg. per 100 cc. for dogs as compared with 250 mg. per 100 cc. for man. Consequently, the cholesterol–phospholipid ratio of the plasma for dogs is much lower, actually averaging 0.49 for dogs as compared with the approximate figure of 0.80 for man. The cholesterol–phospholipid ratio of the alpha lipoproteins is about the same in the two groups. The cholesterol–phospholipid ratios of the fractions presumably containing beta lipoproteins in dogs are approximately the same as those of the alpha lipoproteins and of the whole plasma and may be compared with the approximate average of 1.25 found for beta lipoproteins in human subjects. This would seem to indicate that the proteins recovered in these fractions in normal dogs are, at least in their lipid composition, quite different from those of man.

Another great difference between dogs and man is in the distribution of cholesterol between the Cohn fractions. One may compare the dog's 83 per cent of the total cholesterol in fractions IV + V + VI with man's approximate 30 per cent. Further observations on dog's plasma will be necessary before it can be definitely stated that this reflects accurately a separation between alpha and beta lipoproteins.

The S_f 10–20 bodies are not found in the ultracentrifuged plasma of normal dogs.

The plasma of rabbits and rats differ in one striking respect from that of the dog. The concentration of total cholesterol is much less. The concentration of phospholipids is also lower, but since it is not proportionately diminished, the cholesterol–phospholipid ratios are somewhat higher than those of dogs although not nearly so high as those of man. The distribution of cholesterol in the rabbit shows a percentage of cholesterol in fractions IV + V + VI lower than in the dog but much higher than that of man. In the rat, no determinations were made of the cholesterol–phospholipid ratios in the fractions of plasma or of the distribution of cholesterol between the fractions.

S_f 10–20 bodies do not appear in the ultracentrifugal patterns of normal rabbits and rats.

In summary it may be said that although the data are far less complete than could be desired, there are many striking differences between the lipid composition of plasma in three mammals which appear to be immune to spontaneous atherosclerosis and that in man who is so seriously predisposed.

TABLE 2.—*Comparison of Lipid Values in Man and Other Mammals. Data of Dogs, Rabbits and Rats are from Unpublished Observations of Dr. Forrest E. Kendall*[37]

	Man	Dog	Rabbit	Rat
Total cholesterol mg. %	200	210	51	67
Phospholipid mg. %	250	430	88	101
Chol./PL. ratio				
Plasma	0.80	0.49	0.58	0.67
Alpha lipoprotein	0.50	0.48	0.37	
Beta lipoprotein	1.25	0.51	0.76	
% total cholesterol in alpha lipoprotein	30	83	53	—
% total cholesterol in beta lipoprotein	70	17	47	—
S_f 10–20 mg. %	12	None	None	None

Variations in the Lipid Composition of Human Plasma

Since all humans do not have the same degree of predisposition to the development of atherosclerosis, it is pertinent to inquire whether the variations in susceptibility are signalized by

differences in the lipid composition of plasma. In attempting an answer, chief interest would naturally be focused upon the values of all the chemical criteria in conditions in which variations in incidence, degree and precocity of atherosclerosis and its complications have been noted in the clinical study of the disease.

A few of the better known clinical peculiarities of atherosclerosis may be mentioned briefly. No human is born with it. The disease is rare or absent in normal childhood. While not absent in all young women, its complications are seldom seen before the menopause. Both in its extent and in the frequency of its complications, the disease becomes more threatening with age. Older men and women appear to be about equally affected. In certain diseases and particularly in diabetes, nephrosis and familial xanthomatosis, atherosclerosis develops early in life and tends to be unusually extensive.

Effect of Age. In table 3 comparison is made between the chemical composition of blood drawn from the umbilical cord of newborn infants with that of blood from young and older adults. It will be seen that in the cord blood the concentration of total cholesterol is low; that of the phospholipids, relatively high. It is also apparent that the cholesterol–phospholipid ratio in the plasma and in the beta lipoprotein is low, that the percentage of total cholesterol in alpha lipoprotein is relatively high, and in the ultracentrifugal patterns no S_f 10–20 bodies are discovered.[38] It thus appears that the plasma withdrawn from the umbilical cord of the newborn infant is strikingly like that of the rabbit and rat.

Information concerning the lipid constitution of the plasma in childhood is incomplete and is therefore not included in the table. Such evidence as is now available indicates that an approximately adult pattern is attained shortly after birth[27] but that the S_f 10–20 bodies are missing or are present in only small amounts.[39]

Younger adults differ from the older individuals moderately but in several respects. The cholesterol concentration is lower, the cholesterol–phospholipid ratio tends to be slightly less, a greater percentage of the total cholesterol is found in alpha lipoprotein, and the S_f 10–20 bodies tend to be in lower concentration.

Effect of Sex. In table 4 differences attributable to sex have been summarized. It will be seen that young men and young women have about equal concentrations of cholesterol, but that in young women the concentration of phospholipid is higher, that the cholesterol–phospholipid ratios tend to be lower, that there is a greater percentage of the total cholesterol in alpha lipoprotein and a lower S_f 10–20 concentration. In contrast to this it is remarkable that the lipid constitution of plasma in men and women past the age of 45 differs but little.

TABLE 3.—*Effect of Age on the Lipid Composition and Distribution of Human Plasma*

	Fetus Cord Blood at Term	Normal Young Men and Women Age 18–35	Normal Older Men and Women Age 45–65
Total cholesterol mg. %	65	190	245
Phospholipid mg. %	123	223	229
Chol./PL. ratio			
Plasma	0.56	0.90	0.98
Alpha lipoprotein	0.43	0.53	0.50
Beta lipoprotein	0.82	1.32	1.36
% total cholesterol in alpha lipoprotein	43.0	29.3	23.1
% total cholesterol in beta lipoprotein	57.0	67.5	75.2
S_f 10–20 mg. %	0	10	15

It would seem then, from the standpoint of analyzable chemical factors, that the newborn baby closely simulates or resembles the rabbit and rat, that sometime during childhood, and perhaps quite early, these characteristics are lost. Among adults, the young healthy woman deviates least from the pattern of newborn babies and immune mammals. Her cholesterol level is about the same as that of the dog; her phospholipid level, while not as high as the dog's is maintained at a higher level than in young men. Her cholesterol–phospholipid ratio is lower than that of men of her own age; she has a greater proportion of her cholesterol in the form of alpha lipoprotein. In these respects she is superior to her brothers, but grossly

inferior to the dog and not so well equipped as the rabbit and the rat.

If any of the chemical features of the blood of mammals can be regarded as protective against the development of atherosclerosis, one must conclude that all so-called normal human adults and indeed all human beings except the newborn are imperfectly and indeed precariously equipped to avoid the disease.

Effect of Diseases Predisposing to Atherosclerosis. In table 5 comparison is made between the chemical state in normal young men and women and that of patients suffering from the conditions such as diabetes, nephrosis and xanthomatosis in which atherosclerosis is known to be precocious and extensive. A glance at the tabulation reveals that hypercholesterolemia is a factor common to all the predisposing conditions. This is, however, by no means the only chemical abnormality. The phospholipid values are also increased although not so greatly as those of the cholesterol. The cholesterol–phospholipid ratios of the plasma tend to be higher than in normal men and women. Relatively little of the total cholesterol is combined with alpha lipoprotein. The cholesterol–phospholipid ratio in the fractions containing beta lipoprotein tends to be higher than normal. The S_f 10–20 bodies of Gofman are often grossly increased.

In brief it may be seen that in these conditions which are known to predispose strongly to presenile and abnormally extensive deposits of lipids in arteries, the pattern of lipid concentration and distribution deviates most widely from those of immune mammals and newborn human infants. They vary significantly from the patterns of the relatively immune young women.

Conditions in Survivors of Myocardial Infarction. The difficulty of recognizing atherosclerosis clinically is notorious. Roentgenologic surveys of the arterial system for abnormal patches of calcification, electrocardiographic studies, ballistocardiographic observations, exercise tolerance tests, and other expedients may be helpful in indicating its presence. No one test, however, is pathognomonic, and all of them together fail to establish proof of the extent or even the presence of the process. Indeed it is quite impossible at present to distinguish between the apparently normal adult and the very atheromatous individual who has not yet suffered recognizable complications of the atherosclerotic lesion. Those who have exhibited myocardial infarction, intermittent

TABLE 4.—*Effect of Sex on the Lipid Composition and Distribution of Human Plasma*

	Normal Women Aged 18–35	Normal Men Aged 18–35	Normal Women Aged 45–65	Normal Men Aged 45–65
Total cholesterol mg. %	187	197	252	239
Phospholipid mg. %	228	195	278	265
Chol./PL. ratio	0.87	0.97	1.00	0.95
% total cholesterol in alpha lipoprotein	34.3	25.2	23.4	22.9
% total cholesterol in beta lipoprotein	61.8	72.0	75.0	75.3
S_f 10–20	5	12	15	15

TABLE 5.—*Effect of Diseases Predisposing to Atherosclerosis on the Lipid Composition and Distribution of Human Plasma*

	Normal Young Men and Women	Survivors of Myocardial Infarction	Nephrotics	Diabetics	Familial Xanthomatosis
Total cholesterol (mg. %)	190	259	577	254	423
Chol./PL. ratio	0.90	1.02	1.28	1.08	1.12
% total cholesterol in alpha lipoprotein	29.3	13.6	5.1	19.1	5.9
% total cholesterol in beta lipoprotein	67.5	83.9	93.8	78.7	93.1
S_f 10–20	10	33	ca 200	ca 30	ca 250

claudication or cerebral thrombosis or other complications may have suffered their disability because of strategically located patches of atheroma. In general their arteries may be freer of atherosclerotic disease than those of persons who have exhibited no symptoms or signs of illness. Under these circumstances the establishment of certainly normal controls among adults is not feasible and the customary selection of survivors of myocardial infarction as examples of advanced atherosclerosis is justifiable only because there is at present no superior alternative.

It is of great interest, however, to examine with all available methods the state of lipids in the plasma of survivors of one or more attacks of myocardial infarction, even though comparison with other apparently healthy individuals may be only partially valid.

For cholesterol concentrations and cholesterol-phospholipid ratios, the data compiled by Gertler, Garn and Lerman[36] are especially valuable because of the careful comparison made by the authors between men who had experienced one or more myocardial infarctions before the age of 40 years and a group of ostensibly normal men of the same age, race and constitution. The mean values and ranges of values for concentration of cholesterol and cholesterol–phospholipid ratios in the two groups are presented in table 6.

It will be seen that the mean values for both the concentrations of cholesterol and the cholesterol–phospholipid ratios are higher in the survivors of myocardial infarction. The range is, however, very large in both groups. The variation in cholesterol concentration for survivors of myocardial infarction from 167 to 490 may be compared with 155 to 455 for the matched controls. The range of cholesterol–phospholipid ratios of 0.58 to 1.32 for the survivors of myocardial infarction approximates that of 0.52 to 1.15 for the matched controls. Closer examination of the data as originally presented by Gertler, Garn and Lerman reveals that 59 per cent of the values for the concentration of cholesterol in the survivors of myocardial infarction fell below 300 mg. per 100 cc., the range in which most of the matched controls were found. It is noteworthy also that 11 per cent of the controls had values of more

TABLE 6.—*Comparison of Cholesterol Concentrations and Cholesterol–Phospholipid Ratios in Survivors of Myocardial Infarction and Matched Controls from Observations of Gertler, Garn and Lerman.*[36]

	Concentration of Total Cholesterol mg.%		Chol./PL. Ratio	
	Mean	Range	Mean	Range
Survivors of myocardial infarction	287	167–490	0.90	0.52–1.15
Matched controls	242	155–455	0.78	0.58–1.32

TABLE 7.—*Comparison of S_f 10–20 Concentration in Survivors of Myocardial Infarction and Presumably Normal Individuals of Similar Age. Data Have been Taken from Gofman's Scatter Diagrams.*[24]

S_f 10–20 mg.%	Normal Women			Normal Men			Myocardial Infarcts Men	
	Age 20–30 %	Age 30–40 %	Age 40–50 %	Age 20–30 %	Age 30–40 %	Age 40–50 %	Age 30–40 %	Age 40–50 %
0–5	79	68	46	47	32	29		6
5–20	17	17	33	31	34	36	33	17
20–40	4	11	18	16	23	21	47	42
40–60		4	3	5	9	10	20	23
60–80				1	1	2		4
80–100					0	1		6
100–120					1	1		2

TABLE 8.—*Comparison of Distribution of Cholesterol between Lipoproteins in Survivors of Myocardial Infarction and Presumably Normal Individuals at Various Ages. Distribution is Indicated by Percentage of Total Cholesterol in Alpha Lipoprotein.*

% Total Cholesterol as Alpha lipoprotein	Women 18–35 %	Men 18–35 %	Women 45–65 %	Men 45–65 %	Survivors of Myocardial Infarction %
5.0– 9.9					22
10.0–14.9		8	10	19	39
15.0–19.9		12	35	38	30
20.0–24.9	10	30	20	19	6
25.0–29.9	15	30	15	14	2
30.0–34.5	25	12	5	6	1
35.0–39.9	35	8	15	14	
40.0–44.9	10				
45.0–49.9	5				

than 300 mg. per 100 cc. A similar situation was evident in the cholesterol–phospholipid ratios where 60 per cent of the survivors of myocardial infarctions had values below 0.96, the ranges in which 90 per cent of the values of the matched controls were found.

It appears that the higher averages for the survivors of myocardial infarction are dependent to a considerable degree upon the high values encountered in less than half of the group and that the remainder of the cases have cholesterol concentrations and cholesterol–phospholipid ratios quantitatively similar to those of the matched controls.

In table 7 data have been taken from Gofman's scatter diagram* for comparison of the concentration of S_f 10–20 bodies in survivors of myocardial infarction with presumably normal controls of different ages. The average concentration of these substances is higher in survivors of myocardial infarction than in any of the normal groups. The range, however, is extremely great in all categories, with many survivors of myocardial infarction displaying values encountered even in normal young women and more frequently in presumably normal men at all ages. Again the averages are influenced to a considerable degree by the occurrence among relatively few survivors of infarction of very high concentrations of S_f 10–20 bodies.

In table 8 a similar summary has been prepared for comparison between survivors of infarction and presumably normal men and women for the distribution of cholesterol between the two types of lipoproteins. It is seen that the mean value of the percentage of cholesterol as alpha lipoprotein is much lower in the cases of infarction. Again, the range for all groups is considerable. It is noteworthy, however, that no presumably normal young woman has shown less than 20 per cent of her total cholesterol in the form of alpha lipoprotein and that very few of the cases of myocardial infarction have shown values above this level.

In summary, it may be said that survivors of myocardial infarction as a group display in their plasmas patterns of lipid concentration and distribution which deviate greatly from those of immune mammals, newborn babies and partially protected young women and which may approach those of conditions like nephrosis, xanthomatosis and diabetes where the predisposition to atherosclerosis is excessive. On the average they have a greater than normal concentration of cholesterol, a higher cholesterol–phospholipid ratio, a smaller percentage of cholesterol in the form of alpha lipoprotein and a higher concentration of S_f 10–20 bodies in the ultracentrifugal pattern.

Examination of the data reveals, however, that the deviations which are so apparent in the group may be entirely absent at the time of examination in not a few of the individuals that compose the group. This discrepancy is more apparent in the cholesterol and S_f 10–20 concentrations and in the cholesterol–phospholipid ratios, but also is encountered occasionally in the distribution of cholesterol between the lipoproteins. It is of sufficiently frequent occurrence to make hazardous the use of any of the criteria for diagnosis or clinical recognition of the presence of atherosclerosis.

It is of interest, however, to attempt some estimate of the relative degree of correlation between the various chemical criteria and the actual incidence of myocardial infarction. In table 9 a comparison of correlations has been set up. In the upper half of the table, the mean values of the various criteria for survivors of myocardial infarction and normal controls have been assembled. In the lower half the degree of correlation has been roughly indicated in two ways: first, as the percentage of survivors of myocardial infarction who show values below the mean for the controls, and second, as the percentage of controls who have values above the mean for survivors of infarction. For the concentration of cholesterol and the cholesterol-phospholipid ratios, use has been made of the tables of Gertler, Garn and Lerman.[36] For the S_f 10–20 bodies we have employed the figures from the scatter diagrams of Gofman,[24] and have taken presumably normal men of ages from 20 to 65 as controls. For the distribution of cholesterol between the two forms of lipoprotein we have used our own data with presumably normal men between the ages of

* Circulation **2**: 166, 1950.

18 and 65 as controls. It should be noted that for convenience in tabulation and comparison we have chosen to use in table 9 the values for the percentage of the total cholesterol in beta lipoproteins.

Examination of the correlation of the various criteria of lipid abnormality shows that with all methods many of the control group exhibit

TABLE 9.—*Comparison of Correlations of Several Abnormalities in the Concentration and Distribution of Lipids with the Presence of Myocardial Infarction. The Upper Half of the Table Shows Mean Values for Concentration of Cholesterol and Cholesterol–Phospholipid Ratios Taken from Gertler, Garn and Lerman[36]; Concentration of S_f 10–20 from Gofman[24]; and Distribution of Cholesterol, Here Indicated as Percentage of Total Cholesterol in Beta Lipoproteins, from Published and Unpublished Results of Barr, Russ and Eder.[29] The Lower Half of the Table Shows Correlations of the Various Methods with the Clinical State.*

	Total Cholesterol mg. %	Chol./PL. Ratio (Gertler et al.)	S_f 10–20 mg.% (Gofman)	Total Cholesterol in Beta Lipoprotein (Barr et al.)
Mean for survivors of myocardial infarction	286	0.90	33	86
Mean for controls	242	0.78	14	76
% survivors below mean for controls	ca 30	ca 30	18	2
% controls above mean for survivors	ca 20	ca 15	13	13

lipid values above the mean for survivors of myocardial infarction. This may indicate that among the presumably normal individuals selected for controls some unrecognized atherosclerotics were included. On the other hand, it appears that in survivors of myocardial infarction the distribution of cholesterol between lipoproteins is more constantly disturbed than are the concentrations of cholesterol or S_f 10–20 bodies or the cholesterol–phospholipid ratios.

Distribution of Cholesterol between Lipoproteins in a Variety of Conditions. In table 10 data from our own published[21, 29] and unpublished observations have been assembled to indicate the relationship of the distribution of cholesterol to physiologic and pathologic states in which there is known to be a variable predisposition to atherosclerosis. Special attention is invited to the second column of the table which presents the means for the per-

TABLE 10.—*Correlation of the Distribution of Cholesterol and of Cholesterol Concentration with Several Conditions in which There is a Variable Predisposition to Atherosclerosis. Distribution Is Indicated in This Table as Percentage of Total Cholesterol in Alpha Lipoprotein.*

Subjects	Number of Subjects	% Total Cholesterol in Alpha lipoproteins		Total Cholesterol Mean mg. %
		Mean	Range	
Normal dogs	14	82.9	76.0–91.4	167
Normal rabbits	2	52.7	50.8–54.6	41
Human infants (cord blood)	27	43.3	28.7–61.0	65
Normal women (age 18–35)	20	34.3	22.2–46.1	187
Normal men (age 18–35)	24	25.2	13.3–39.4	197
Normal women (age 45–65)	20	23.4	11.7–38.4	252
Normal men (age 45–65)	21	22.9	12.4–40.7	239
Young diabetics (age 4–35)	19	19.1	5.6–37.7	254
Survivors of myocardial infarction	85	14.1	5.6–30.4	258
Atherosclerotic rabbits (Kellner)	3	9.6	7.0–16.4	364
Familial xanthomatosis	6	7.1	3.2–14.0	459
Atherosclerotic dogs (Kendall)	6	5.8	1.1– 8.1	2698
Nephrotics	12	5.1	1.8– 8.7	577

centage of total cholesterol in alpha lipoproteins and to the third column where the range of values for each group of subjects is presented. In column 4 the mean concentration of cholesterol for each of the groups is included to indicate the relative degree of correlation of this criterion with clinical and experimental conditions relating to atherosclerosis.

The first three groups of subjects in the table, namely, normal dogs, normal rabbits and human newborn infants[41] may be regarded as immune to atherosclerosis. Next in order are the normal young women who seldom

exhibit the complications of the disease and who have a somewhat lower percentage of cholesterol as alpha lipoprotein than young men. The values for men and women past the age of 45 differ little from each other, but are higher than the values for younger groups, which is in accord with their greater tendency to atherosclerosis. Next on the list come the diabetics, a mixed group in which many extremely abnormal patterns are encountered even among younger subjects. The averages for survivors of myocardial infarction are still lower than those of the diabetics. Of great interest are the rabbits of Kellner[34] which were made artificially atherosclerotic by feeding cholesterol, and the dogs of Kendall in which atherosclerosis was produced by combining the administration of thiouracil with a high intake of cholesterol.[40] The low values for these atherosclerotic animals may be compared with the quite high percentages of cholesterol in alpha lipoproteins exhibited by normal rabbits and dogs. Still lower in the scale are the percentages for patients with familial xanthomatosis and nephrotics in whom the alpha lipoprotein, as indicated by the percentage of cholesterol, becomes extremely low even though the total cholesterol is greatly elevated.

Although in general, higher concentrations of cholesterol (table 10, column 4) are encountered in conditions in which atherosclerosis is present, the correlations with the disease and its tendency are obscure.

Modification of the Chemical Composition of Plasma by Artificial Means

We may now consider the last main question of this discussion. Is it possible that presumably undesirable characteristics of the chemical composition of plasma in man can be modified by therapeutic agents?

One of the striking phenomena of lipid composition and distribution is a considerable degree of constancy in each individual through a considerable range of variations in life's situations. This is in contrast to the wide range of values for all lipid constituents in different individuals of a group. With maintenance of health, a man or woman who on first examination reveals a high value for total cholesterol and a low percentage of cholesterol in alpha lipoprotein, will continue to display approximately the same values over long periods. The same generalization may be applied to those who have initially low values of cholesterol and high values of alpha lipoprotein. The composition and distribution of lipids are, however, not immutable. Clinical states such as infections, Graves' disease, myxedema, biliary cirrhosis, biliary obstruction, hepatitis and pregnancy may produce in a relatively short time great changes in the lipid pattern.

If the abnormalities of lipid composition and distribution associated with atherosclerosis are to be regarded as relevant to its pathogenesis, one of the goals of any therapeutic procedure would be to alter it in the direction of conditions found in young women or in immune mammals such as the dog, rabbit, and rat.

Our own interest has been chiefly centered on the action of sex hormones. It was at first stimulated by the question of why young women have less tendency to complications of atherosclerosis than young men and why this difference is no longer apparent after the menopause. It was further encouraged by our discovery that young women have more of their cholesterol in the form of alpha lipoprotein than young men. It was thought possible that the mere presence of circulating estrogens in considerable amounts might affect the concentration or distribution of lipids.

As subjects for a test of this idea we chose survivors of myocardial infarction. We gave to each of them estrogen in the form of either Estinyl or Premarin in oral dosages of 10,000 rat units,[30] an amount which was sufficient to produce after two to three weeks changes in the size of the breasts and a temporary loss of sexual desire and potency. The response in the lipid patterns of the plasma was much greater than had been anticipated. In every instance there was an increase in the percentage of cholesterol in alpha lipoprotein and a corresponding reduction in the percentage of cholesterol in beta lipoprotein. There was a marked fall in the cholesterol–phospholipid ratio of the whole plasma and in the fraction containing

beta lipoproteins. In most cases there was also a fall in the concentration of total cholesterol in the plasma. The values finally obtained were approximately those of young healthy men. When the medication was discontinued the concentration and distribution of lipids returned promptly to their previous levels. The direction and degree of change are illustrated in the following tables and figure.

TABLE 11.—*Effect of Estrogen Administration on the Concentration and Distribution of Cholesterol in the Plasma of Survivors of Myocardial Infarction.*

Stage of Treatment	Total Cholesterol mg. %	Cholesterol in Alpha lipoproteins		Cholesterol in Beta lipoproteins mg. %
		% of total	mg. %	
Before	282	11.3	32	250
After 1 week	283	16.7	41	243
2 weeks	270	17.5	47	223
3 weeks	260	19.0	49	211
4 weeks	251	21.0	53	198
5 weeks	247	22.0	55	191
6 weeks	225	25.4	57	168
7 weeks	222	25.0	56	166
8 weeks	216	26.0	56	160
9 weeks	210	27.1	57	153

TABLE 12.—*Effect of Estrogen Administration on the Cholesterol–Phospholipid Ratios of Plasma and Its Fractions in Survivors of Myocardial Infarction.*

	Cholesterol–Phospholipid Ratios		
	Plasma	Alpha lipoproteins	Beta lipoproteins
Before estrogen administration	1.05	0.47	1.32
At end of estrogen administration	0.72	0.42	0.97

In table 11, the average effects of continued estrogen administration on the concentration and distribution of cholesterol are presented. It will be seen that the action is cumulative over several weeks after which it tends to reach a plateau.

In table 12 the effects of estrogen on the cholesterol–phospholipid ratios in plasma and in alpha and beta lipoproteins have been summarized. It will be seen that the ratio in the alpha lipoproteins remains unchanged while that in the plasma falls from an average of 1.05 to an average of 0.72, and the ratio in beta lipoproteins falls from an average of 1.32 to 0.97, a level lower than is encountered in normal adults.

In table 13, the changes in distribution and concentration of cholesterol accompanying the withdrawal of estrogen are presented. In every instance there was an increase in the concentration of total cholesterol and a diminution in the form of alpha lipoprotein. These changes were abrupt and usually resulted in a return of the values to levels observed before the administration was begun.

TABLE 13.—*Changes in the Distribution and Concentration of Cholesterol Following Withdrawal of Estrogen in Survivors of Myocardial Infarction.*

Time	Cholesterol Concentration mg. %	% Total Cholesterol in Alpha lipoproteins	Total Cholesterol Concentration in Beta lipoproteins mg. %
At end of estrogen administration	218	26.8	158
2 weeks later	285	18.5	220
Difference	67	8.3	62

TABLE 14.—*Effects of Administration of Methyl Testosterone on the Concentration and Distribution of Cholesterol in Human Plasma.*

Subject	% Total Cholesterol in Alpha Lipoproteins		
	Before Testosterone	After Testosterone	After Withdrawal of Testosterone
Po	8.8	5.2	11.1
Ia	16.0	11.1	21.4
Ma	18.0	10.7	16.7
Cr	18.1	8.7	17.3
Ra	18.9	13.6	23.8
Cu	21.5	12.1	23.3
Wa	26.1	15.9	22.0
Bi	27.1	16.1	26.7
Gu	27.6	13.3	20.4
La	27.9	21.6	24.3
Ba	28.4	18.3	28.4
Ru	35.4	26.4	30.0
Average	22.8	14.4	22.1

In figure 1 the effects of administration and withdrawal of estrogen may be followed during two cycles of treatment in a man who had survived myocardial infarction. The upper

limit of the shaded area of the chart represents the concentration of total cholesterol; the shaded area itself, the concentration of cholesterol in alpha lipoproteins; the lower limit, the concentration of cholesterol in beta lipoproteins. The figures seen immediately below the shaded area represent the varying percentages of cholesterol in alpha lipoprotein.

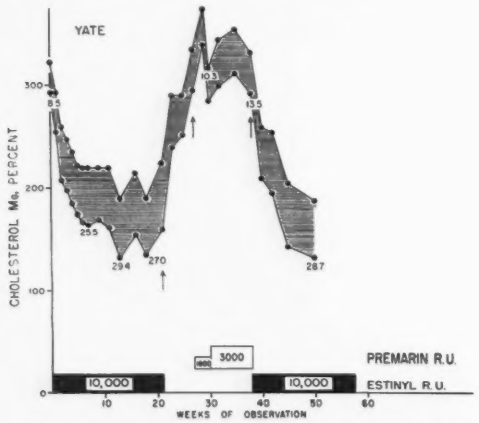

FIG. 1. Effects of administration and withdrawal of estrogen in a survivor of myocardial infarction. The upper limit of the shaded area represents the concentration of total cholesterol; the shaded area itself, the concentration of cholesterol in alpha lipoproteins; the part below the shaded area, the concentration of cholesterol in beta lipoproteins. The figures placed immediately below the shaded area are percentages of total cholesterol in alpha lipoproteins.

The effects observed with estrogens stimulated observations on the action of testosterone which will be reported later from our laboratory in some detail.[42] For the tests, we used methyl testosterone, usually in daily doses of 50 mg. In table 14 its action is shown in 12 miscellaneous cases. It will be seen that there were changes in distribution opposite in direction to those observed following administration of estrogen.

In survivors of myocardial infarction we have also been able to show that methyl testosterone will promptly reverse the effects of estrogen. Of considerable interest are observations in which the effect of estrogens and testosterone are compared in the same patient.

In figure 2 the effects of combined action of the two substances may be followed. The observations were made on a man of 53 with only 9.7 per cent of his cholesterol in the form of alpha lipoprotein. The method of charting is similar to that used in figure 1. In the first portion of the figure, the usual effect of estrogen may be observed. It is notable that it could be maintained with reduction of the dosage from 10,000 to 2500 rat units of Estinyl. The action of daily doses of 50 mg. of methyl testosterone

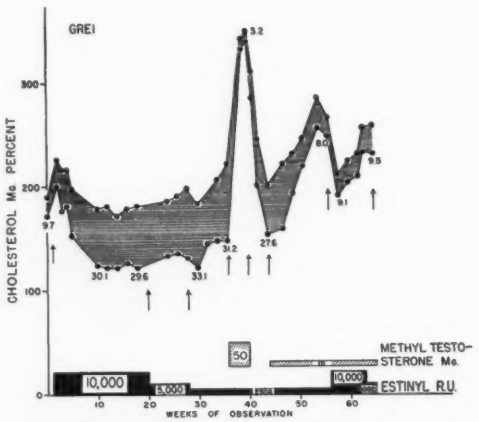

FIG. 2. Effects of estrogen and methyl testosterone in a survivor of myocardial infarction. The method of representation is the same as in figure 1.

introduced at a time when the estrogen administration was being continued is dramatic and extreme. At its height the cholesterol in alpha lipoprotein constituted only 3.2 per cent of the total. The action disappeared and the estrogen effect was again realized as soon as the testosterone dosage was discontinued. It is notable also that a similar but not such an extreme neutralizing effect of the testosterone was later observed during the daily administration of only 10 mg. of methyl testosterone.

The observations of the action of sex hormones are regarded as important for several reasons. They show that the concentration and distribution of lipids are subject to hormonal influence. They indicate that there may be a chemical reason for the apparent partial immunity of young women to the complications of atherosclerosis. They demonstrate that the abnormal pattern of lipid distribution encountered in most survivors of myocardial infarction can be manipulated and, by the

use of estrogens, can be changed to values more appropriate to young men and women. The action of methyl testosterone suggests that it might not be a desirable medication in patients who have extensive atherosclerotic disease.

Summary

In this lecture a partial and tentative examination has been made of chemical factors possibly important in the pathogenesis of atherosclerosis. The discussion has centered about four observations concerning the incidence and extent of the disease. The first is that man appears to be unique among mammals in his predisposition; the second, that the condition is seldom if ever seen in the human infant at birth; the third, that healthy women are not likely to develop its complications before the time of the menopause; the fourth, that in man certain maladies and particularly diabetes, familial xanthomatosis, and nephrosis favor early and extensive atheromatous deposits.

An attempt has been made to relate present knowledge of lipid composition of the blood to known variations in the degree of predisposition to the disease. This has included scrutiny of observations on concentration of cholesterol and the S_f 10–20 bodies of Gofman, on cholesterol–phospholipid ratios and on the distribution of cholesterol between the lipoproteins of plasma.

It has been shown that in mammals which never develop spontaneous atherosclerosis the values of all the criteria of concentration and distribution of lipids differ from those of man. Among human beings only the infant at birth has plasma which in its lipid composition closely resembles that of immune mammals. In young women the deviation is less than in other human adults. In groups of patients that display the greatest tendency to the development of atherosclerosis, the plasma lipid patterns differ most widely from those of other mammals.

Among survivors of myocardial infarction many but not all display striking abnormalities in every one of the criteria of lipid concentration and distribution. Comparison of the different methods indicates that in survivors of infarction the distribution of cholesterol between the lipoproteins is more constantly disturbed than the other chemical factors. No test however deviates with sufficient constancy to permit its use in the clinical diagnosis either of the presence of atherosclerosis or of a tendency to its development.

It has been shown that the lipid patterns in man are not immutable but can be manipulated to a considerable degree. Specifically, it has been demonstrated that the administration of estrogen can convert the highly pathologic patterns of survivors of myocardial infarction to normal adult human values, and that the use of methyl testosterone exaggerates the chemical pathology of myocardial infarction and may even produce deviant patterns in those who have been previously normal.

Although the observations which have been reviewed offer strong evidence that predisposition to atherosclerosis is related to deviations in the lipid composition of the blood, they do not establish the chemical hypothesis of pathogenesis. Although at present they lead to no practical applications in therapy, they are regarded as worthy of further investigation with a justifiable hope that greater knowledge may offer new clues to prevention and control.

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Facts and Fallacies Regarding the Blood Pressure of Different Regional and Racial Groups

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The blood pressure cuff reveals higher values in complex societies than in simpler social environments. Evaluation of the importance of this fact necessitates a more exact use of such terms as "high blood pressure" or "hypertensive disease" as applied to an individual, and "mean blood pressure" or "incidence of hypertension" as applied to groups. The inadequacies of the cuff method of blood pressure determination are particularly evident in group studies. From the available facts, a few cautious conclusions may be drawn.

THE blood pressure of people of so-called primitive cultural environments has been reported to be lower than that of people in more complex societies.[1-17] Negroes in the United States have a higher blood pressure than the whites,[18-35] while Negroes in Africa[1-2, 15-17, 36-37] and Chinese in China[6-7, 9, 38-45] have been reported to have exceptionally low blood pressure. These facts, if true, should be of importance in evaluating current concepts of the etiology of hypertension. The authors' findings in Panama confirm earlier reports[46-49] of a high incidence of hypertension in the Negro population and a moderate to low incidence among the whites and Panamanians. The literature was reviewed in an attempt to correlate the data from Panama with the prevailing views regarding the blood pressure of different racial and cultural groups. This review revealed variables and discrepancies usually not considered in earlier studies, which cast doubt on the generally accepted concepts mentioned above. Full consideration has been given to these variables in the presentation of the accompanying material which has, of necessity, been obtained mostly from the reports of other investigators. Only those data which should reflect the relative blood pressure of distinct racial, geographical, economic, sociologic, or cultural groups have been used.

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RELIABILITY OF DATA

There are many pitfalls to be avoided in interpreting comparative blood pressure data. As many of these as possible were determined and considered, although, unquestionably, there were others which were not recognized.

The manner of determining and reporting blood pressure in these studies has varied with the type of apparatus used, the size of the arm cuff, the method of determining the systolic pressure (auscultatory or palpatory), the change of tone or disappearance of all sounds selected as indicating the diastolic pressure, the care with which basal pressure was determined, and other factors. Age, weight, sex, and other factors known to affect blood pressure were not always reported. In few reports could it be determined whether the hypertension reported was "essential" or otherwise. Although Smith[50] showed that in the United States high blood pressure is only rarely due to renal disease, this is not necessarily true of other groups of people.

The terms "high blood pressure" and "hypertensive disease" are not synonymous. The difference may be much greater than is ordinarily indicated. It is not necessarily true that the pathologic changes frequently associated with hypertension are due to the elevated blood pressure because it is known only that under most conditions these changes and high blood pressure are concomitant variables. Snapper[51] has reported "hypertensive disease" in Chinese with "normal blood pressure." In interpreting Snapper's observations, it is important to know

that due to variations in the size of the arm, blood pressure by the auscultatory method varies 60 mm. Hg as compared with the true blood pressure obtained by intra-arterial cannulation.[52-54] This fact has been ignored by other investigators in evaluating the blood pressure of different groups of people.

The term "blood pressure" alone when applied to a group means little. In order to compare relative values in different groups, it is necessary to choose one factor to which the various terms for blood pressure can be converted. Blood pressure for a group may be expressed in the following ways: (1) Mean blood pressure: the arithmetic mean of all blood pressures. (2) Mean normal blood pressure: the arithmetic mean of all blood pressures except those that are "abnormal." (3) Incidence of "hypertension": the frequency of hypertension as a clinical or pathologic entity. Each of these expressions has objectionable features. "Mean blood pressure" varies greatly with the number of "hypotensives" or "hypertensives" included in the series. On the other hand, "mean *normal* blood pressure" can be low although the incidence of "hypertension" is high. Since arbitrary criteria for "hypertension" based on blood pressure determinations are not applicable to different groups, statements regarding "mean normal blood pressure" have little meaning. For these reasons, it was felt that the most desirable data was the "incidence of hypertension."

Unfortunately, it was impossible to use only the reports that could be converted to one factor and still have adequate material from which to draw conclusions. Consequently, comparisons were made of mean blood pressure with mean blood pressure, incidence of hypertension with incidence of hypertension, and mean normal blood pressure with mean normal blood pressure. When adequate collateral data such as age, sex, weight, and method of determining blood pressure were included in the reports, the error in the comparison was believed to be small. The likelihood of error was decreased by indicating only how one group compared with another and using only comparative terms such as "higher," "lower," or "comparable" instead of numeric values. Considering these points, extensive summary tables of quantitative data were omitted from this report. It was usually impossible to analyze the data statistically.

Caucasians

Thorough studies in the United States[55-59] giving mean blood pressure, mean normal blood pressure, and incidence of hypertension for age, weight, and sex were used for comparison with other reports. They were compared first with people of predominantly white stock living under circumstances differing markedly from those in the United States. Indian insurance applicants in India,[60-61] Indian laborers in Upper Assam,[62] and white men in the Virgin Islands[30] had mean blood pressures comparable to the figures for inhabitants of the United States while Arabs in the Euphrates Valley[63] and Indians in Calcutta[64] had relatively low values. Charity hospital patients in Egypt had a low incidence of hypertension while private patients had a moderate incidence[65] compared with that in the United States. Indians in the Royal Air Force in India had lower mean blood pressure than the British under the same circumstances but were also much lighter in weight.[66]

A number of authors,[67-73] have suggested that the blood pressure of whites in the tropics and the Orient is lower than the pressure of white persons living in other climates. Mason[74] has summarized this subject and concludes that there was a slight tendency toward lowering of blood pressure in tropical climates but that individual variation was very great. Many of these reports were based on data from the Philippines. Siler[75] found an apparently lower blood pressure in the Philippines, but when he corrected for weight found no difference for those 10 or more pounds overweight. Harris[76] questioned Foster's observations in China on the basis of life insurance statistics. Harris felt that the mean blood pressure level and incidence of hypertension of Americans and Europeans in China were comparable to those found in Western countries. Others[30, 66, 77-80] have also failed to find a tropical climate to have any significant effect on blood pressure.

Mongoloids

Chinese. Low mean blood pressures as compared with that of inhabitants of the United States have been consistently reported for the Chinese in China,[6, 7, 9, 38-45] Japan[81] and Formosa.[82] Krakower[83] found values for Chinese in Canada to be lower than the United States figures but higher than for Chinese in China. Hunter[81] and Tung[84] found a relation similar to that found by Krakower between the values for Chinese in the United States and Chinese in China. Ling[85] in extensive data on insurance applicants found the mean blood pressure of the Chinese in China to be comparable to that in other reports on Chinese, but his incidence of hypertension was surprisingly high. The low mean blood pressure in the presence of many hypertensives was due to a large number of hypotensives (2.26 per cent had blood pressure below 90/60) and quite likely to a lower mean *normal* blood pressure.

Ling's interpretation of the phenomenon of low blood pressure in China and high blood pressure in North America, based on the marked difference in the weights of the two groups, warrants more attention. For a given age and height, the mean body weight of Westerners is 11 to 23 pounds (10 to 20 per cent) greater than that of Chinese in China. Ling demonstrated a progressive increase in mean blood pressure with increasing weight when his material was divided into four groups according to the relation of the weights of his subjects to the mean weight for Chinese. Symond's figures for mean blood pressure in the United States[59] are lower than for Ling's most obese group but higher than all other groups.

When Symond's figures (10 to 20 per cent overweight by Chinese standards) are compared with Ling's group 3 (20 to 40 per cent overweight by Chinese standards) and both are grouped according to age, the differences between the blood pressures are insignificant. Ling stated that contrary to the general belief that the blood pressure of the Chinese is 20 to 30 mm. Hg less than that of Westerners, the systolic is only 5 to 13 mm. lower and the diastolic is only 4 to 8 mm. lower. Ling calculated the incidence of hypertension (blood pressure greater than 150 systolic and/or 100 diastolic) for only two groups: those overweight ("other than the standard") and those underweight. Of those overweight, 21.8 per cent had hypertension in contrast to only 0.1 per cent of those underweight. Ling concluded, "It is not my intention to claim that lighter body weight is the sole factor in the causation of relative hypotension in Chinese. Nevertheless, the results seem to indicate that relative underweight is the most important and certain factor."

Ling's conclusion must be accepted, but other factors which vary concomitantly with weight (such as social and dietary habits and emotional factors) may also play a role in the incidence of hypertension. However, of unquestionable importance is the fact that blood pressure as determined by the cuff method becomes greater with increasing circumference of the arm.[52-53] This fact appears more important in view of Snapper's[51] observations of hypertensive disease in Chinese in the absence of notable elevation of blood pressure. He pointed out that hypertensive disease was not rare in China and the symptomatology as regards heart failure, cerebral hemorrhage, and eyeground changes (he included reports of malignant hypertension) was the same as is seen in the West. The only differences were the relatively low blood pressure and the lack of arteriosclerosis and myocardial infarction. He found that hypertension was the most frequent cause of cardiovascular disease in the older age groups.

Wang[44] had a similar experience. He described 58 cases of "essential hypertension" seen in the Hsiang Ya Hospital in Changsha over a period of three years. All but two of these had complications which were responsible for their admission to the hospital. 80.2 per cent had cardiac enlargement. Half of these had cardiac decompensation. The high incidence of complications suggests the possibility of many others having hypertension which was undetected because the blood pressure was not determined routinely or because of the inadequacy of the cuff method. He states, "Hypertensive cardiovascular disease is a fairly common clinical occurrence." It is unfortunate that extensive postmortem material is unobtainable

in China since it would help clarify the true incidence of hypertensive disease.

In general, the data support Ling's contention that weight is the most important variable which has been detected to account for the differences in the recorded blood pressure of Chinese and Westerners in either the West or China. It must be added that in the authors' opinion, the mechanical error in the determination of blood pressure by the indirect method in persons of widely differing arm circumference is the most certain factor responsible for this correlation.

Since differences in body build do not appear to account for all of the differences in mean blood pressure reported for Chinese and Westerners, other factors are probably involved. Moreover the mechanical error in blood pressure determination by the cuff method may not explain all of the correlations found between mean blood pressure and body build. Thus obese people may prove to have a higher mean blood pressure, even when determined by arterial cannulation. Even if this is found to be so, it could not be concluded that obesity and hypertension are causally related since a common factor may be inducing both conditions.

Other Mongoloid People. Reports of mean blood pressure for Koreans,[86] Marshall Islanders,[87] Caroline Islanders,[10] Eskimos,[8, 14, 88] Zuni Indians,[3] Mexicans,[89] Yucatecans[12-13, 90] Guatemalans,[13] Panamanians,[46] San Blas Islanders,[5] and Puerto Ricans[72, 91-92] indicate lower values than for those living in the United States. Most reports indicate a moderately high mean blood pressure for the Japanese.[93-97] However, Hunter,[81, 98] found the Japanese to have lower mean blood pressure in Japan than in the United States. One of the present authors has seen definite cases of hypertension with characteristic retinopathy in rural Mayan villages of Guatemala.[99] Most of the above reports fail to give data relative to the age-height-weight relationship of these people. However, since all the difference between the blood pressure values for Chinese and those for people of the United States could not be accounted for on the basis of body build, it appears that mean blood pressure of Mongoloids is lower.

Negroes

It is unfortunate that most of the references indicating low blood pressure in Africa are without supporting data. When these are eliminated most of the other reports indicating low blood pressure are from Kenya.

Donnison's findings[1, 2] are the most frequently quoted. That his data are not representative of the Negro in all of Africa is obvious from some of the subsequent reports. Donnison apparently took exceptional precautions to obtain the lowest possible blood pressure in his subjects. Each subject prior to determination of the blood pressure had an examination, "to exclude any condition that might influence blood pressure." The mean blood pressure thus determined was comparable to the United States values for subjects under 40 years, but much lower than United States values for older men. The fact that the younger men were recruits for labor while a tour of native reservations was necessary to find a sufficiently large number of older subjects may possibly explain this result. Donnison mentions that, "nervous subjects not uncommonly had systolic pressures over 200 temporarily," but that, "it was very uncommon to see systolic pressures greater than 144 that persisted." The low mean blood pressure reported does not exclude a moderate incidence of hypertension since we do not know the mean normal blood pressure for these people or the number of "hypotensives."

Jex-Blake[37] saw only one case of cerebral hemorrhage (this case was attributed to syphilis) in 1100 autopsies in Kenya and concluded that hypertension must be rare. Vint[15] found from postmortem material that all cardiovascular disease caused only 5.6 per cent of deaths. Heimann and co-workers[36] found a low incidence of hypertension in a clinical and postmortem study of 120 cases of heart disease in Negroes in the city of Johannesburg, but blood pressure determinations were not made in all cases and the criteria for autopsy diagnosis were not given. Becker[100] later, in a careful study of postmortem material, revealed an unquestionably high incidence of hypertension in Negroes in Johannesburg. Brock[106] also felt that obesity and hypertension were probably more common in Cape Colored females than in European females.

Several reports from other parts of Africa indicate a high incidence of hypertension. Dubois[101] found high blood pressure levels in a "primitive" village of the Belgian Congo, but in his recent book[102] commented, "Hypertension is rare in the tropics." In so doing he mentioned the prevailing view because he regarded the matter as unsettled.[103] Beheyt,[104] working in the Belgian Congo, considered the incidence of hypertension to be high in Leopoldville. Williams[16] reported a high incidence of hypertension in Ugandi, but in a later study[17] of 66 hospital cases found that all but 16 had syphilis, gonorrhea, nephritis, or polycystic kidneys. It seems unlikely that these conditions could have accounted for more than a small percentage of the hypertension previously reported. Colyer[105] found a high incidence of hypertension in Northern Rhodesia.

As noted above, most reports from Africa indicate a high incidence of hypertension with the exception of those from Kenya. It should be pointed out that the population of Kenya has contributed little to the ancestry of the Negroes in the New World who are, for the most part, descendents of West Africans. The Negroid people of Kenya are mixed with the Hamitic people, a linguistic rather than racial group, who are of mixed black and white stock.

Hicks and Matters,[4] and Nye[11] reported low blood pressure in Australian aborigines, but Hicks and Matters[4] pointed out that in their study the weight varied from 42 to 63 Kg. They also commented on the poor state of nutrition.

Many reports,[18-35, 49] confirm the high incidence of hypertension found in the Negro in the New World. It is higher than in the whites in the same area in every instance.

The situation in Panama is so unique that it deserves discussion. Several observers using different methods have noted the blood pressure to be high in Negroes and moderate to low in whites and Panamanians.[46-49] Marvin and Smith[47] pointed out that of patients admitted to Gorgas Hospital in the Canal Zone with hypertensive cardiovascular disease as their primary condition, 94.1 per cent of Panamanians and 83.3 per cent of West Indians (Negroes) had abnormal urine. Thirty per cent of Panamanians and 17 per cent of West Indians had elevated blood nonprotein nitrogen. Taylor[48] in a study of autopsy material found that of subjects with hypertension, 12 per cent of Negroes and 18 per cent of whites had normal kidneys while all Panamanians had some type of nephritis. Taylor interpreted this as suggesting that the Negroes do develop essential hypertension while the Panamanians may not since all had nephritis.

The cases studied at Gorgas Hospital are composed of Panama Canal and Panama Railroad employees and their families. The Negroes and Panamanians work under comparable circumstances and wage scales. Their diets do not differ significantly according to careful survey.[107] Neither group is characterized by either obesity or undernutrition although we have found Negro women attending the prenatal clinic of Gorgas Hospital to be larger and heavier. Their fundamental personality type has never been systematically evaluated, but they differ in that the Panamanians are native citizens of Panama while the Negroes studied were brought in from the West Indies as temporary charges of the United States Government, and were neither natives nor citizens of either Panama or the United States.

How all this affects the Negro psychologically cannot be stated; but to postulate that environmental and cultural factors are the major cause of their higher blood pressure would require demonstration of a low incidence of hypertension in Africa, where the Negroes are in a position somewhat comparable to the Panamanian in Panama. However as mentioned above, the reports of Becker,[103] Coyler,[105] Dubois,[101] Brock,[103] and Williams[16] establish that African Negroes do have considerable hypertension, even when in their native state.[16, 101, 105]

Since differences in body build do exist between Negroes and Panamanians, this factor probably accounts for part of the differences in average blood pressure observed. Although psychologic and social factors may account for some of the difference in incidence of hypertensive disease between these racial groups, it is at least equally probable that genetic factors are of primary importance.

Comment

In an effort to determine the validity of the beliefs regarding the comparative blood pressure of people living in so-called primitive and civilized environments, reports that might clarify the problem were collected and analyzed. This material is difficult to evaluate because the studies fail to control all of the variables known to affect blood pressure.

One major variable in particular, change in arm size with change in body weight and its effect in increasing or decreasing the blood pressure reading obtained by the cuff method, undoubtedly influences much of the recorded data. The intra-arterial blood pressure is the only satisfactory measure for comparing the blood pressure of people of differing weights. For these reasons, future studies of "normal" blood pressure, fall in blood pressure with starvation, amelioration of hypertension in the obese with weight reduction, the benign course of hypertension in the obese, and differences in blood pressure with age and sex, of prisoners and prison guards, of rural and urban people, and in different disease states should include data referable to the size of the arm and intra-arterial values when possible.

Until more is known of the relation of blood pressure and hypertensive disease, a normal range of blood pressure will be difficult to define and direct comparison of blood pressure values in different groups may not correctly indicate the relative incidence of hypertensive disease.

Despite the many difficulties in interpreting such data some cautious conclusions can be drawn. Certainly people in very simple social environments sometimes have hypertension. Most of the other conclusions that have been drawn regarding differences in blood pressure of different groups of people must be considered to be poorly substantiated because of a failure to consider pertinent variables. There does appear to be a racial difference in blood pressure values which cannot be accounted for entirely by the variables which were considered. Even this difference, however, may not be due to genetic factors since the members of a race, regardless of where they are, may retain cultural traits or be subjected to environmental stresses which cause an increase or decrease in blood pressure.

Conclusions

1. If proper consideration is given to known variables, the evidence to prove that geographic or cultural environments have a significant effect on the incidence of essential hypertension is inadequate.

2. While the data show that racial differences in the incidence of hypertension do exist, they do not suffice to indicate the relative importance of genetic, psychologic and social factors.

3. Much more uniform and exacting methods for studying and reporting the blood pressure of groups are needed in future epidemiologic studies of blood pressure.

Sumario Español

El esfigmomanómetro revela valores mas altos en sociedades complejas que en ambientes sociales sencillos. La evaluación de la importancia de este hecho demanda un uso más exacto de términos como "alta presión arterial" o "enfermedad hipertensa" cuando se aplican a un individuo y "presión arterial promedio" o "incidencia de hipertension" cuando se aplica a grupos. Lo inadecuado de las determinaciones de presiones con el esfigmomanómetro de bocamanga es particularmente evidente en estudios de grupos. Algunas conclusiones cautas se pueden desprender de los hechos asequibles.

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Platelet Thrombosis Syndrome

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This paper reports the clinical and pathologic manifestations of seven cases of platelet thrombosis syndrome. Evidence is presented to indicate that vascular damage precedes the formation of platelet thrombi. It is suggested that the syndrome may be secondary to a variety of underlying disease entities.

THE PURPOSE of this paper is to report the clinical and pathologic manifestations of seven cases of the platelet thrombosis syndrome. In 1925 Moschowitz[1] first described a rapidly fatal disease characterized by fever, anemia, petechiae, neurologic signs and autopsy findings of generalized capillary and arteriolar hyaline thrombi. Since then approximately 45 cases have been reported,[2-30] most of them within the past 10 years. Many synonyms for the disease have been suggested, such as "thrombotic thrombocytopenic purpura,"[11] "thrombocytic acroangiothrombosis,"[8] "thrombotic microangiopathic hemolytic anemia,"[26] "disseminated arteriolar and capillary platelet thromboses,"[17] and "generalized blood platelet thrombosis."[14] Much of this nomenclature is either cumbersome or suggests features of the disease that are not invariably present. We believe the term "platelet thrombosis syndrome" to be the most satisfactory until the nature of the entity is more fully elucidated.

CASE REPORTS

Case 1. A 21 year old white male student was admitted to the Presbyterian Hospital on May 8, 1936, with a six months' history of increasing weakness and anemia following an upper respiratory infection. The only significant feature of his previous history was albuminuria for the past five years. Physical examination revealed jaundice, pallor, petechiae, retinal hemorrhages, hepatomegaly, blood pressure 150/76, and temperature of 100 F. Hemoglobin was 25 per cent, red blood cells 1 million, reticulocytes 43 per cent; anisocytosis, poikilocytosis, and polychromatophilia were present. Red blood cell fragility began at 0.425 and was complete at 0.350. White blood cells numbered 3400 (neutrophils 49, lymphocytes 32, monocytes 8, eosinophils 2, basophils 2, and myelocytes 6). Platelets numbered 9,000.* Capillary fragility was 30 cm. Hg. Bleeding time was 7 to 40 minutes. Coagulation time was 3.5 minutes. Urine showed 3 plus albuminuria, occasional red blood cells, white blood cells and casts. Nonprotein nitrogen was 48. Serum bilirubin (indirect) was 4 mg. per 100 cc. Serum proteins were 6.1 Gm. per 100 cc. (albumin 4.2, globulin 1.9). Bone marrow aspiration revealed hyperplasia with prevalence of erythroblasts in all stages.

Throughout the three month hospital stay the anemia proved refractory to multiple transfusions, iron and liver therapy. On August 1, 1936, the red blood cells were 1.66 million, serum bilirubin was 11.3 mg. per 100 cc. and blood urea nitrogen 73 mg. per 100 cc. The patient died with a terminal septicemia from an abscess in the buttock. The gross findings at autopsy revealed ascites, hydropericardium, bilateral hydrothorax, splenomegaly (500 Gm.), hepatomegaly (2000 Gm.), scattered petechial hemorrhages, abscess of buttock, abscesses of heart, adrenal, kidney and prostate, infarct of spleen, a chronic gastric ulcer, edema of the lungs, and a vegetation on the aortic valve.

Case 2.† A 44 year old white male iron-worker was admitted to the hospital on Nov. 12, 1937, with a history of exposure to lead. For the preceding three weeks he had complained of severe headaches, weakness, tinnitus, deafness in the right ear and epigastric distress following meals. On the day before admission he had a transitory episode of aphasia. Physical examination revealed pallor, mental confusion and a right facial weakness, blood pressure 130/90, and temperature 99 to 100 F. Hemoglobin was 42 per cent, red blood cells 2 million with anisocytosis, poikilocytosis and marked basophilic stippling; reticulocytes were 19 per cent. Erythrocyte sedimentation rate was 38. White blood cells numbered 11,300 (neutrophils 78, eosinophils 5, basophils 3, monocytes 8 and lymphocytes 6). Platelets numbered 46,000. Red blood cell fragility began

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* The direct method of counting platelets was used on all occasions.

† Cases 1 and 2 have been reported briefly by I. Gore.

at 0.450 and was complete at 0.30. Bleeding time was two minutes, clotting time 4 minutes, 45 seconds. Capillary fragility test was normal. Serum proteins were 6.9 Gm. per 100 cc. (albumin 3.7, globulin 3.2). Nonprotein nitrogen was 33. Serum bilirubin was 2.5 mg. per 100 cc. The Kline test was negative. The cerebrospinal fluid was normal. Urine contained a trace of albumin and many red cells.

A few days after admission petechiae and scleral icterus were noted. He finally became comatose with occasional tonic and clonic convulsions. The anemia failed to respond to transfusions, and bleeding from the gums, hematuria and temperature of 104 F. were present. He expired five days after admission. Gross findings at autopsy revealed scattered petechial hemorrhages, edema of the lungs, a spleen of 280 Gm., a liver of 1800 Gm., and a chronic gastric ulcer. Chemical analyses revealed excessive amounts of lead in viscera and bones.

Case 3. A 32 year old white housewife was admitted to the hospital on Oct. 27, 1940, with a history of transient rash on the hands two months previously. Four days before admission she developed severe epigastric pain, weakness and petechiae of the skin; these symptoms had persisted. She was mildly disoriented on the day of admission. Physical examination revealed pallor, petechiae, scleral icterus, blood pressure 105/80 and temperature of 101.6 F. During the examination she became unconscious and had a convulsion. Hemoglobin was 7 Gm. per 100 cc., red blood cells 2.15 million; anisocytosis, poikilocytosis, polychromatophilia and nucleated red cells were present. White blood cells numbered 21,640 (neutrophils 77, lymphocytes 20, myelocytes 2). Platelets numbered 50,000. Nonprotein nitrogen was 39. Serum bilirubin was 4.8 mg. per 100 cc. The Kline test was negative. The urine contained albumin and red cells.

The patient never regained consciousness and died four hours after admission. Gross findings at autopsy revealed scattered petechial hemorrhages, a spleen of 140 Gm., a liver of 1420 Gm., and two acute ulcerations of the stomach.

Case 4. A 16 year old white schoolgirl was admitted to the hospital on April 26, 1942, with a history of headaches associated with double vision for the preceding 10 days. On the day of admission she experienced a sudden left hemiparesis. Physical examination revealed a left hemiparesis, a systolic murmur at the apex, blood pressure 118/70, and temperature of 99 F. Hemoglobin was 11.6 Gm. per cent, red blood cells 4.3 million with anisocytosis and poikilocytosis. White blood cells numbered 5,750 (neutrophils 71, lymphocytes 21, monocytes 5, eosinophils 3). The platelets numbered 270,000. Nonprotein nitrogen was 39 mg. per 100 cc. The cephalin flocculation was 2 plus. Prothrombin time was 52 seconds. Serum proteins were 7.6 Gm. per 100 cc. (albumin 4.8, globulin 2.8). The erythrocyte sedimentation rate was 60 mm. in 1 hour. The Kline test was negative. The urine examination was negative.

During the hospital stay of eight weeks there was a constantly elevated erythrocyte sedimentation rate, a mild anemia and nonspecific electrocardiographic changes of myocardial damage. The prothrombin time gradually decreased to normal by June 15, 1942. Repeated platelet counts were performed, the lowest count recorded being 143,000. On May 21, 1942, the patient experienced a sudden arterial occlusion to the right lower leg; return of weak pulsations followed paravertebral sympathetic block. On June 16, 1942, she became unconscious suddenly and experienced several convulsive episodes. She died the following day without regaining consciousness. The gross findings at autopsy revealed a vegetation on the mitral valve, a spleen weighing 160 Gm., with two infarcts, a liver of 1400 Gm. and mottled myocardium and kidneys.

Case 5. A 40 year old white housewife was admitted to the hospital on Nov. 4, 1947, with a 10 weeks' history of weakness and nausea. More recently she had experienced severe headaches and mental confusion. Physical examination revealed slight icterus, retinal hemorrhages, blood pressure 100/60 and temperature of 100 F. Hemoglobin was 7.3 Gm. per 100 cc. and red blood cells numbered 2.25 million with anisocytosis, poikilocytosis and basophilic stippling. White blood cells numbered 6,500 (neutrophils 57 and lymphocytes 43); there were 4 nucleated red blood cells per 100 white blood cells. Reticulocytes were 10 per cent. The cephalin flocculation was 4 plus, the thymol turbidity 3 plus. Red blood cell fragility began at 0.60 and was complete at 0.325. Serum icteric index was 9 units. Serum bilirubin was 1 mg. per 100 cc. There were no isoagglutinins at 37 C. Platelets numbered 10,000. The Kline test was negative. No anti-Rh agglutinins were demonstrable; there were questionable blocking antibodies (repeated). The urine contained albumin and red cells.

Soon after admission, aphasia, mental confusion and severe weakness of the extremities were prominent features. The hemoglobin fell to 4.6 Gm. per 100 cc.; the white count rose to 11,500 (neutrophils 79, lymphocytes 20, and monocytes 1). Despite multiple blood transfusions, folic acid and liver extract, the anemia remained refractory and she died four weeks after admission. The gross findings at autopsy revealed many scattered petechial hemorrhages and splenomegaly (320 Gm.).

Case 6. A 44 year old Mexican man was admitted to the hospital on May 10, 1952, with a long and complex history of variable neuromuscular complaints over the preceding seven years. One year ago his blood pressure began to rise and reached 200/100. Three months ago he became ataxic, with vertigo, headaches, nausea and vomiting, diplopia and

anesthesia of the left side of his face. Physical examination revealed flaccidity of the extremities, ataxia, dysarthria and hypertensive retinopathy, apical murmur suggestive of Austin-Flint, blood pressure 200/100 and temperature of 99.2 F. Hemoglobin was 14 Gm. per 100 cc. The erythrocytes sedimentation rate was 75 mm. in 1 hour. White blood cells numbered 7,100 (neutrophils 68 and lymphocytes 25). The urine contained 4 plus albumin and 10 to 15 red blood cells and 20 to 30 white blood cells per high power field. Nonprotein nitrogen was 61 mg. per 100 cc. The cephalin flocculation was negative. Serum proteins were 6.8 Gm. per 100 cc. (albumin 3.5, globulin 3.3). The cerebrospinal fluid was normal.

He deteriorated rapidly with rise in temperature, aphasia and stupor, and expired May 18, 1952. The gross findings at autopsy revealed vegetations of the mitral and aortic valves, a spleen weighing 110 Gm., a liver weighing 1900 Gm., each kidney weighing 170 Gm., finely granular, mottled and hemorrhagic, and cerebral petechiae.

Case 7. A 37 year old housewife was admitted to the hospital on Aug. 6, 1952, with a three months' history of progressively severe headaches, vertigo and diplopia. Two days before admission she experienced two brief convulsive episodes and had been disoriented and restless since. Physical examination revealed scattered petechiae, retinal hemorrhages, blood pressure 200/150 and temperature of 102 F. Hemoglobin was 8.7 Gm. per 100 cc. and red blood cells numbered 3.27 million. Red blood cell fragility began at 0.44 and was complete at 0.30. The erythrocyte sedimentation rate was 83. Platelets numbered 24,000. White blood cells numbered 8,400 (neutrophils 94 and lymphocytes 6). Later the white blood cells numbered 35,000 (neutrophils 97 and lymphocytes 3). Nonprotein nitrogen was 31 mg. per 100 cc. Prothrombin time was 22 4 seconds. The Coombs test was negative. Serum bilirubin was 0.3 mg. per 100 cc. The urine contained albumin and red cells.

Massive hematuria commenced soon after admission. An electrocardiogram revealed recent myocardial damage. Her condition rapidly deteriorated, with further convulsive episodes, and she expired on Aug. 10, 1952. The gross findings at autopsy revealed hypertrophy of the left ventricle, focal myocardial infarct, vegetations on the mitral valve, splenomegaly (380 Gm.) with scattered infarcts, hepatomegaly (2200 Gm.), hemorrhagic kidneys and hemorrhagic cystitis.

Summary of Clinical Features

The average age of these patients was 33 years. There appeared to be no obvious sex or racial predilection. The average duration of the entire illness was 17 weeks; occasionally, however, vague prodromal symptoms were present for several weeks before the onset of the acute illness. Case 1 had an unusually long illness lasting nine months; case 6 presents difficulty in differentiating the lengthy history of neuromuscular disorders from the more recent central nervous system disease.

Fever, in the 99 to 102 F. range, was a constant feature. Hemorrhagic manifestations, noted in five cases consisted of purpura, retinal hemorrhages, hematuria or bleeding gums and epistaxis. In cases 4 and 6 no hemorrhagic manifestations were present; in case 4 no thrombocytopenia was detected; and in case 6 platelet counts were not performed. Pallor, weakness and easy fatigability were notable in the five cases with severe anemia, four of whom were jaundiced. Six patients had neurologic findings such as headaches, drowsiness, mental confusion, convulsions, focal paresthesia and paresis. In cases 6 and 7 hypertension was marked but, apparently, preceded evidence of the final illness, at least in case 6. Laboratory examinations revealed a severe normochromic anemia in five cases and minimal anemia in cases 4 and 6. Anisocytosis, poikilocytosis, reticulocytosis, and nucleated red cells were frequently present. Serum bilirubin levels were elevated in four cases. Coomb's test was negative in case 7, but blocking antibodies were questionable in case 5. Red blood cell fragility studies were normal in four cases examined. Elevation of the erythrocyte sedimentation rate was a common finding. There was a leukocytosis with a "left shift" in four cases; in case 1, however, persistent leukopenia with "left shift" was present. A severe thrombocytopenia was present in five cases; a platelet count was not performed on case 6. Of unusual interest is the fact that platelet counts in case 4 were repeatedly within normal range with an unexplained transient prolongation of prothrombin times. The Kline or Wassermann test was negative in all cases. Positive cephalin flocculation and thymol turbidity tests were found in two of three cases examined. The blood proteins were estimated in four cases, hyperglobulinemia being present in two (the cephalin flocculation and thymol turbidity tests were negative in one, and not performed in the other). Of the four patients

without concomitant renal disease, two had increased nonprotein nitrogen blood levels and hematuria. Of the three cases with concomitant renal disease, two had elevated nonprotein nitrogen blood levels; all three had albumin and red cells in the urine. The cerebrospinal fluid of three patients was normal. Electrocardiographic studies were performed on three cases and evidence of acute myocardial damage was found in two.

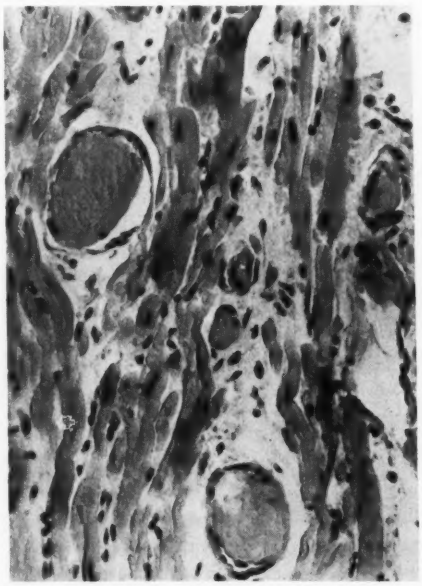


FIG. 1. Photomicrograph (hematoxylin and eosin, × 250) showing myocardium with characteristic hyaline thrombi in capillaries.

SUMMARY OF POSTMORTEM FINDINGS

Significant gross findings were scant. Occasional areas of hemorrhage, vegetations on the heart valves, focal areas of visceral necrosis, particularly in the brain, and splenomegaly were the only gross features that could be related specifically to the syndrome.

Microscopically, the most characteristic finding was the widespread presence of hyaline thrombi in the small arteries, arterioles, and capillaries. (See fig. 1.) These platelet thrombi were present in the kidneys and myocardium in all cases. Involvement of these organs was usually widespread. Markedly dilated, thin-walled vessels containing thrombi were characteristically seen in these two organs. (See fig. 2.) On the basis of serial sections in cases studied by Orbison[33] these dilated vessels were considered to be aneurysmal dilatations and were regarded as evidence for primary vascular damage. In the myocardium many arterioles and capillaries were filled with platelet thrombi in various stages of organization. These were often associated with minimal to abundant

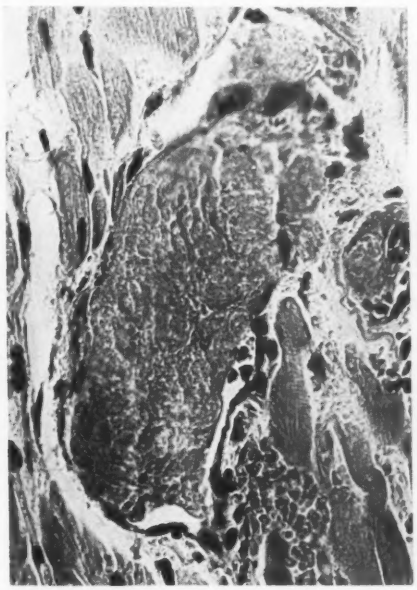


FIG. 2. Photomicrograph (hematoxylin and eosin, × 500) showing dilated vessel (aneurysm) with hyaline thrombus in the myocardium.

endothelial proliferation. (See fig. 3.) In adjacent areas, the myocardium exhibited foci of necrosis and fibrosis. In addition to the myocardial changes, hyaline thrombi were found on the aortic and mitral valves in three cases. These vegetations differed in no respect from the usual picture of thromboendocarditis. Bacteria were not present, and there was no associated inflammatory process. There was eosinophilic degeneration of the valve substance adjacent to the thrombi. (See fig. 4.) It appeared that this eosinophilic degenerated material was extending from the valve surface. Others have reported similar findings on the heart valves.

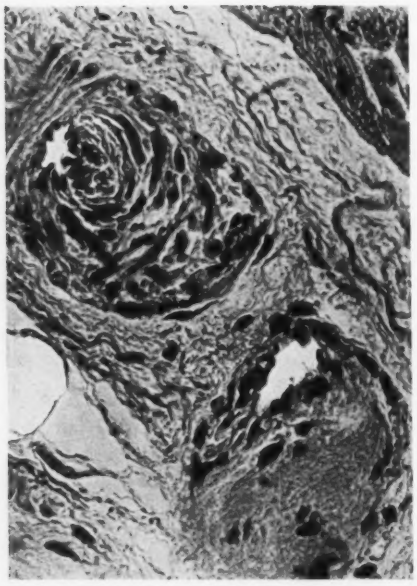


FIG. 3. Photomicrograph (hematoxylin and eosin, × 250) showing organization of thrombus and endothelial proliferation in myocardial vessel. Another vessel shows eosinophilic degeneration which extends into surrounding tissue.

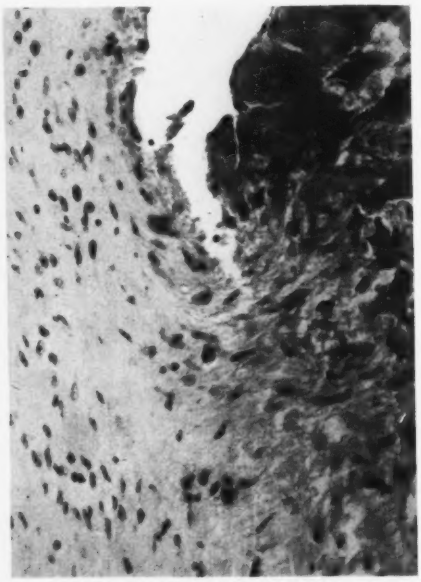


FIG. 4. Photomicrograph (hematoxylin and eosin, × 180) showing aortic valve leaflet with eosinophilic degeneration and attached hyaline vegetation.

In the kidneys, the cortical vessels were commonly the site of platelet thrombi formation. Especially affected were the afferent arterioles with occasional extension of the process into the glomerular tufts. Foci of cortical hemorrhage with red blood cells filling the tubules were occasionally observed. In one case, intercapillary glomerular nephritis

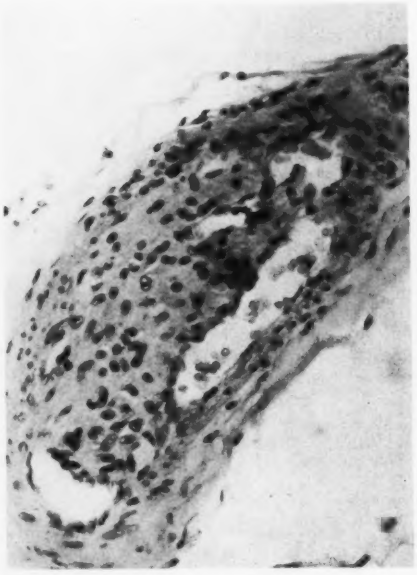


FIG. 5. Photomicrograph (hematoxylin and eosin, × 250) showing organizing thrombus with endothelial proliferation in vessel of pia arachnoid.

was present. What the relationship is between the glomerular nephritis and this syndrome is not clear. Two other cases with marked hypertension had advanced arteriolar nephrosclerosis. Endothelial proliferation in the glomerular tufts was present in still another case. In none of the postmortem material was there anything suggestive of the changes seen in lupus erythematosus.

Brain examinations were performed in three cases, but the presence of neurologic manifestations in all but one of the seven patients would indicate that the brain was involved to the same degree as the kidneys and the heart. The brains that were examined contained widespread involvement of numerous vessels with

platelet thrombi. As in the other sites, endothelial proliferation was present. (See fig. 5.) In one case where the lesions were most widespread, there were numerous gross areas of encephalomalacia. Vessels in the pia arachnoid were similarly involved.

Next in frequency of involvement were the pancreas, adrenals, spleen, and gastrointestinal

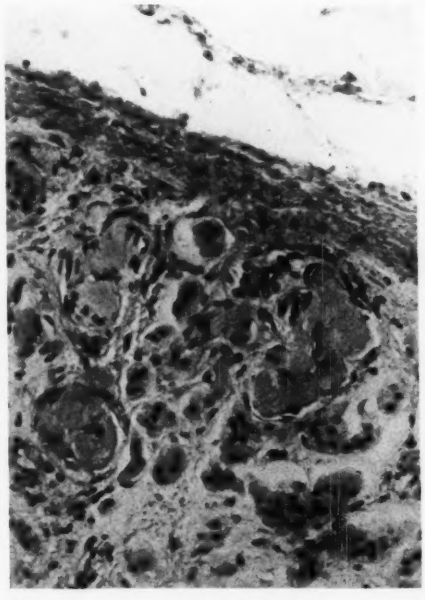


FIG. 6. Photomicrograph (hematoxylin and eosin, × 250) showing adrenal cortex with thrombi in capillaries just beneath the capsule.

tract (six out of seven cases). However, the number of vessels implicated was considerably less than in the previously mentioned sites. There were numerous thrombi in the adrenals, limited almost entirely to the vessels immediately beneath the capsule. (See fig. 6.) Occasionally vessels outside of the capsule contained thrombi. Focal hemorrhages were present. In the pancreas, the involvement was diffuse and generally located in those vessels in the interlobular connective tissue. No secondary changes were present in the pancreas. In the spleen, only few vessels were involved. Splenomegaly was present in four cases. There was considerable congestion and in two cases there were splenic infarcts. There was no

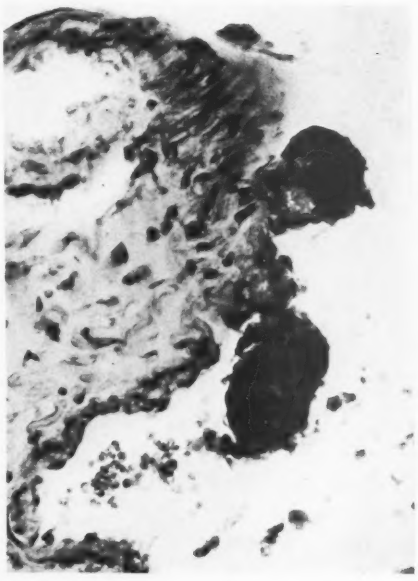
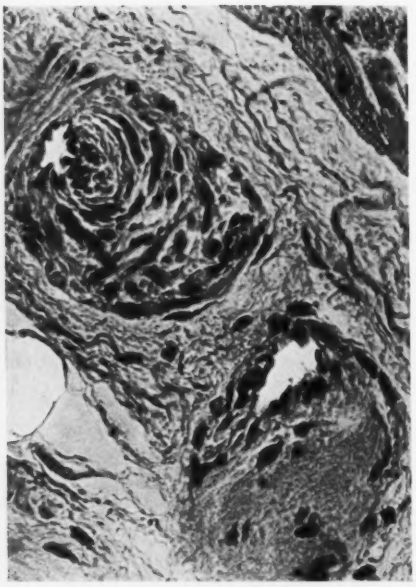


FIG. 7. Photomicrograph (hematoxylin and eosin, × 250) of large pulmonary vessel with small hyaline thrombi attached to intimal surface.

FIG. 8. Photomicrograph (hematoxylin and eosin, × 250) of vessel in myocardium with prethrombotic lesion and superimposed endothelial proliferation.



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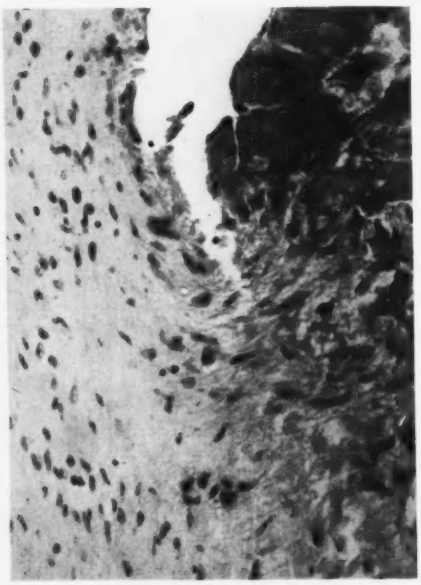

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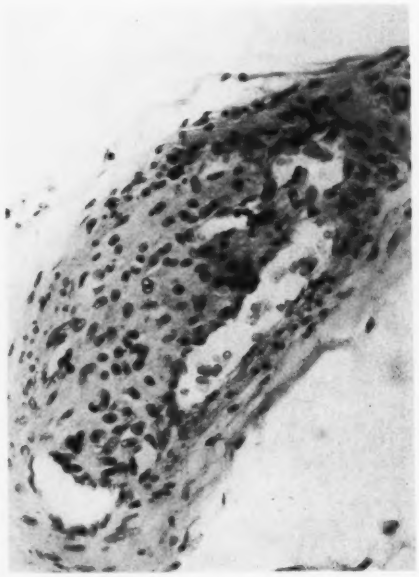

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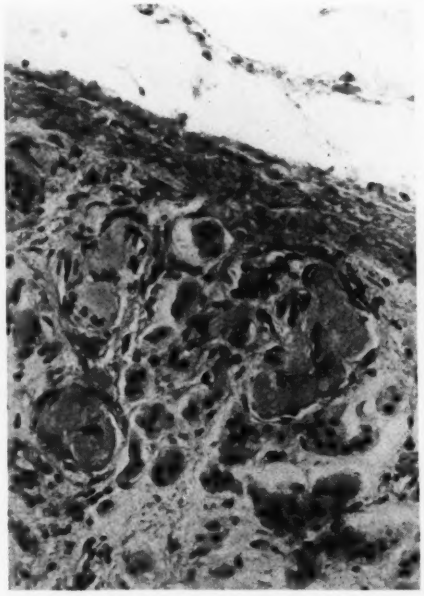

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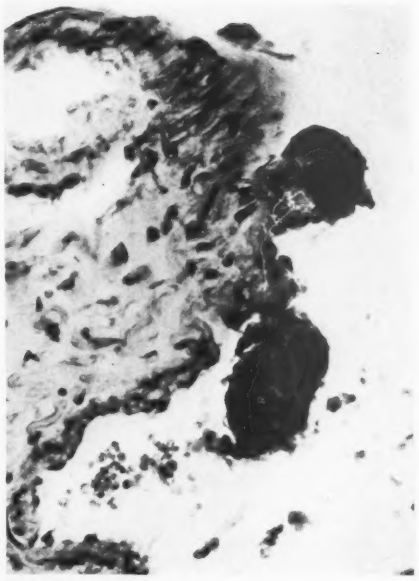

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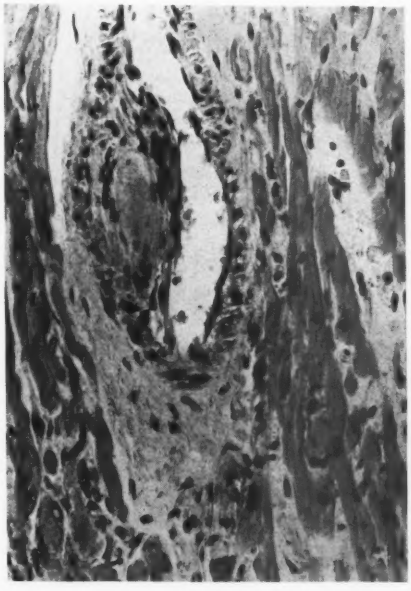

FIG. 8. Photomicrograph (hematoxylin and eosin, × 250) of vessel in myocardium with prethrombotic lesion and superimposed endothelial proliferation.

concentric perivascular fibrous proliferation. Megakaryocytes were infrequent.

In the gastrointestinal tract, the vessels in the submucosa were the ones usually containing thrombi. Foci of hemorrhage were observed. Three cases revealed gastric ulcers (two chronic and one acute). It is possible that the development of these ulcers was related to the vascular occlusions.

Particularly significant was the limited involvement of the lungs and liver. Of the major organs, these were the least frequently involved, and when thrombi were present, it was only in an occasional vessel. In the liver, the usual site was the vessels in the portal region, whereas in the lung there was no characteristic site. The involvement of one vessel in the lung was of considerable interest. It was a considerably larger vessel than those usually seen with platelet thrombi. Attached to its intimal surface at several separate points were small hyaline thrombotic masses. (See fig. 7.) The lumen was not obliterated. This type of involvement would tend to support the view that the vascular change is primary. Megakaryocytes were present in the lungs in three cases.

Other sites in which vessels contained thrombi were the thyroid, pituitary, gallbladder, larynx, diaphragm, urinary bladder, peripheral nerves, tonsils, and striated muscle. It is interesting that striated muscle has only been rarely implicated.

The bone marrow in all cases was uniformly hyperplastic. Abundant megakaryocytes were found and the changes in the marrow were considered consistent with those seen characteristically in secondary anemia. The vessels in the marrow did not contain hyaline thrombi.

A careful search was made for the prethrombotic vascular changes described by Gore.[17] In several instances, these changes were unmistakably identified (fig. 8) and would support the thesis that vascular changes procede the formation of the thrombi. The widespread nature of the process without marked localization to those areas most susceptible to stagnation of the circulation has already been referred to as an argument against this syndrome originating primarily as an intraluminal phenomenon.

Discussion

The etiology of the entity is unknown. It is not even clear whether this condition can be regarded as a primary one or secondary to a variety of underlying diseases. The present evidence supports the view that the thrombi follow vascular damage and is in keeping with the observation of similar changes in known hypersensitive reactions. Platelet thrombi associated with vascular damage have been observed in fatal cases of drug sensitivity reactions.[10, 13] Four of the cases in this study had associated processes which could have produced vascular damage (lead poisoning, glomerulonephritis, and malignant hypertension). In other reports, platelet thromboses have been seen in lupus erythematosus and polyarteritis.[31, 32] On occasion, platelet thrombi are seen in the myocardial arterioles in rheumatic heart disease. Thus, it is entirely possible that this syndrome is not a primary and independent disease.

Summary

1. The clinical and necropsy findings in seven cases of "platelet thrombosis syndrome" have been presented.

2. The findings of this study favor the view that vascular damage precedes the thrombus formation.

3. The view is presented that this syndrome may be entirely secondary to a variety of underlying disease entities.

Sumario Español

En este trabajo se informan las manifestaciones clínicas y patológicas en siete casos del síndrome de trombosis de plaquetas. Se presenta evidencia que indica que el daño vascular precede la formación del trombo de plaquetas. Se sugiere que el síndrome puede ser secundario a una variedad de enfermedades subyacentes.

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Studies on the Control of Hypertension by Hyphex

I. Effects on Blood Pressure

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This report is the first of a series on a method for treatment of hypertension by oral hexamethonium chloride and hydrazinophthalazine. When strictly followed blood pressure was maintained at reasonable or normal levels in 80 per cent of 258 cases of severe hypertension. The malignant stage, when present, was reversed. Renal insufficiency and severe cerebral atherosclerosis limit the effectiveness of the method for prolongation of life.

A METHOD effective for sustained control of the elevated arterial pressure of chronic hypertensive disease has been developed and employed in over 250 patients since August 1951.[1-4] The purposes of the investigation were (1) to ascertain whether or not treated hypertension was compatible with a return to health in patients suffering from its effects; (2) to determine whether or not the method was "specific" in the sense that pathogenetic and secondary influences were favorably altered; (3) to define the limits of the method in terms of severity of disease and alterations toward normal; (4) to detect late "toxic" effects or new diseases caused by the agents employed; and (5) to discover what hazards, if any, accompanied alterations of long standing cardiovascular abnormalities.

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Hyphex is a contraction of the words *hydrazino-phthalazine* and *hexamethonium*, used for convenience in describing the method.

This method was first reported at the 2nd International Gerontological Congress, September 9, 1951; later to the 24th Annual Meeting of the Central Society for Clinical Investigation, November 2, 1951, and at the Scientific Sessions of the 25th Annual Meeting of the American Heart Association, Cleveland, Ohio, April 19, 1952.

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Because the use of any method for treatment of hypertension is controversial, and because the present one has shown conclusively that sustained control can be achieved, we are reporting our experiences in detail. This report deals only with alterations of elevated arterial blood pressure in a series of cases selected for representing as severe forms of arterial hypertension and its complications as have been encountered in a general hospital. The accompanying communication deals with fatal and serious conditions caused by the agents employed.[5] Others will discuss special problems, such as congestive heart failure, angina pectoris, malignant hypertension, renal insufficiency and the effects of poor management.

METHOD

The method is based on the assumption that at least two influences act concurrently to cause generalized vasoconstriction and hypertension[6]; therefore both must be counteracted simultaneously if elevated arterial pressure is to be controlled. One influence is presumably neurogenic, acting through the medium of the autonomic sympathetic nerves. The ideal drug for counteracting this influence is a true sympatholytic agent; unfortunately none so far has been encountered which could be tolerated for months and years of continuous use. Therefore ganglionic blockade by quaternary ammonium salts was utilized. Hexamethonium chloride serves the purpose well,

can be taken orally with safety under certain precautions, and is nontoxic in the sense that "side effects" are the result of its primary action. Sympathetic nervous inhibition is achieved, however, at the expense of parasympathetic nervous inhibition, which can at times be distressing. The drug is excreted rapidly in the urine and therefore must be taken at frequent intervals.[7] No case of severe hypertension encountered has been controlled adequately by this agent alone.

The second influence is presumably nephrogenic and concerns bloodborne vasoconstrictor substances. Of these, pherentasin is one positively identified in hypertensive arterial blood.[8] 1-Hydrazinophthalazine is a true antihypertensive agent of moderate potency[9]; it acts as a carbonyl reagent, binds heavy metals and sulfhydryl compounds and possibly combines directly with the carbonyl group of pherentasin.[10] In large doses it has the property of abolishing the vasopressor actions of certain, but not of all, primary amines. It can be taken orally for indefinite periods of time. When first given, it can exhibit "side effects" due probably to its primary action on other systems than those concerned in hypertension; when the action of the autonomic nerves is inhibited, side effects are lessened. It is excreted fairly rapidly and therefore must be taken at regular intervals.[7] Few cases of severe hypertension encountered have been controlled adequately by this agent alone.

The method is as follows[11]:

The patient must be in hospital. Blood pressure is measured in the supine position every four hours, day and night. Renal function is estimated by the 15, 30 and 60 minute excretion of intravenously injected phenol red (P.S.P.) and the nonprotein nitrogen level of the blood, renal pathology by intravenous pyelography and the state of the urine, cardiac pathology by electrocardiography and x-ray, the state of the blood vessels by funduscopic examination. Hexamethonium chloride is given by mouth and increased to effective levels at a rate depending upon one's estimate of the severity of the hypertension, its lability, and the amount of vascular damage, especially cerebral. Every effort is made to "undershoot" the dose, and to build up toward the desired effect. Dosage schedule is changed daily, slowly, and carefully, depending upon the record of the previous day. 1-Hydrazinophthalazine is added *later*. A typical schedule for a case of severe arterial hypertension without renal insufficiency or marked cerebral atherosclerosis follows:

1st day—125 mg. hexamethonium chloride every four hours. Omit dose if systolic pressure is below 140 mm. Hg.

2nd day—250 mg. hexamethonium chloride every four hours

3rd day—375 mg. hexamethonium chloride every four hours

4th day—500 mg. hexamethonium chloride every four hours. Omit part or all of dose, depending upon level of systolic pressure, as described below.

5th day—Same plus 25 mg. 1-hydrazinophthalazine every four hours

6th day—Same plus 50 mg. 1-hydrazinophthalazine every four hours

7th day—Same plus 75 mg. 1-hydrazinophthalazine every four hours

8th day—Same plus 100 mg. 1-hydrazinophthalazine every four hours

The establishment of normotension would interrupt and stabilize the above schedule at any point.

Routine orders are as follows: (1) Measure blood pressure before each dose (every four hours) and record on graphic chart. (2) Give —— mg. (full dose) of hexamethonium chloride if systolic pressure is 140 mm. Hg or above. (3) Give —— mg. (½ dose) of hexamethonium chloride if systolic pressure is between 130 and 140 mm. Hg. (4) Give —— mg. (¼ dose) of hexamethonium chloride if systolic pressure is between 120 and 130 mm. Hg. (5) Omit all hexamethonium chloride if systolic pressure is below 120 mm. Hg. (6) *Do not omit* 1-hydrazinophthalazine. (7) Give cascara and milk of magnesia or other mild laxatives every evening if no bowel movement that day. Do not allow patient to become constipated. Do not use "bulky" laxatives or "roughage." Use irritative and saline laxatives. Citrate of magnesia is given in the morning if the evening laxative is not effective. It is essential that the patient have a bowel movement every day. (8) Use urecholine for distention, severe constipation and retention of urine in the bladder. (5–10 mg. by mouth. Do not give parenterally as severe reactions may occur; the parasympathetic nervous system is probably sensitized to peripherally acting cholinergic drugs.)

In the most severe cases, the dose of hexamethonium chloride may be increased to 1.0 Gm. every four hours and of 1-hydrazinophthalazine to 200 mg. every four hours; 750 mg. and 150 mg., respectively, per dose will be adequate to control over 90 per cent of cases. At these levels severe constipation may be intolerable unless bowels are kept open daily.

A few days prior to discharge from hospital, the doses given at 2 or 4 a.m. are omitted; generally this results in a slight rise in the blood pressure taken at 6 or 8 a.m. The patient or a member of the family is instructed in the use of the sphygmomanometer,

and measures his own blood pressure before each dose, checking the readings frequently with an experienced observer. At home, he follows the same regimen, with drugs at four hourly intervals, except for one interval at night; the dose of hexamethonium chloride is omitted or reduced according to the prevailing level of systolic pressure. If blood pressure cannot be conveniently measured (as at work), the patient may estimate hypotension by standing quietly for a minute in order to induce faintness. It is essential that the full dose of hexamethonium chloride not be taken when the systolic pressure is normal; hypotension will follow within two hours and distressing reactions may result. The analogy of the control of diabetes with insulin and the control of hypertension with Hyphex is obvious.

Material

All patients were accepted for treatment because hypertension had been severe, persistent, had failed to respond to the usual methods or had caused secondary damage to heart, brain or kidneys. The presence of persistent chronic hypertension had been well documented in every case. For example, 25 suffered from congestive cardiac failure; 43 exhibited various degrees of renal insufficiency with retention of nitrogen in their blood; 35 had suffered one or more cerebral vascular accidents, 35 a coronary occlusion; 12 exhibited signs of deterioration consistent with cerebral atherosclerosis and 8 were severely ill with acute cerebral edema. Their ages ranged from 6 to 80 years; the majority were in the fifth and sixth decades of life, although those exhibiting the malignant stage (89 cases) tended to be younger. Most patients were referred either by other physicians, or in some instances, by patients themselves under treatment; a few had been followed for several years in the outpatient department. No individual whose blood pressure fell with rest in bed and sedation to sustained systolic levels below 180 mm. Hg and diastolic levels below 120 mm. was accepted for treatment. Of the first 100 patients, all showed signs of severe disease and were handicapped by it to various degrees; of the second 150, the requirements for treatment were broadened to include some individuals exhibiting only electrocardiographic evidence of cardiac abnormalities, roentgenographic signs of cardiac enlargement, slight diminution of renal function or severe headaches without definite secondary pathology. It was believed at the beginning of the study that the most vigorous test of the method should be made in advanced cases in order to define the limits of effectiveness. All of our experience, which of necessity includes serious reactions occurring during pioneering attempts now avoided, will be reported in this series of papers.

Method of Analysis

Blood pressure was measured every four hours in hospital by competent nurses and charted. At home, blood pressure was measured by the patient or a member of his family five times a day and charted. Since the levels measured by physicians may be considerably higher than those obtained by nurses and technicians in certain individuals, a comparison was made between "nurses' levels" and "patients' levels" rather than between those obtained by physicians and patients, which would have made the alterations appear greater. "Resting" levels were included in those measured at 2 a.m. and 6 a.m.

The initial stage of the hypertensive disease present in each individual was estimated according to standards which we have found useful. Since some of the secondary effects of hypertension, such as coronary arterial occlusion and cerebral accident, are not directly caused by hypertension but rather are the result of atherosclerosis, and since treatment is aimed at control of blood pressure at as normotensive levels as feasible, atherosclerotic complications were not considered in evaluation of the stage of hypertensive disease. The various stages pertinent to this study are as follows*:

II. *Moderate Benign Hypertension.* Blood pressure always elevated at rest in bed but falls to normal levels during heavy sedation with Sodium Amytal. Ocular fundi, grade I or II (Keith-Wagener). Renal function as measured by the 15 minute excretion of phenol red (P.S.P.) normal or nearly normal (25 per cent or greater). Diastolic pressure usually 105 to 120 mm. Hg, systolic, 180 to 220 mm. during rest in bed.

III. *Severe Benign Hypertension.* Blood pressure not falling to normal during sleep induced by Sodium Amytal. Ocular fundi, grade I or II. Renal function normal or depressed without retention of nitrogen in blood. Diastolic pressure usually 120 to 160 mm. Hg; systolic 200 to 270 mm. during rest in bed.

IV*a*. *Early Malignant Hypertension.* Diastolic pressure always 130 to 160 mm.; systolic 200 to 280 mm. Renal function reduced but without retention of nitrogen in blood. Ocular fundi, grade III. Albuminuria and abnormal microscopic elements present.

IV*b*. *Severe Malignant Hypertension.* Diastolic pressure always 130 to 200 mm. Hg; systolic 200 to 300 mm. Borderline renal func-

* Stage I represents mild benign hypertension, the blood pressure being at normal levels during complete rest, the systolic varying from 150 to 180 mm. Hg and the diastolic 90 to 105 mm. during activity. Stage 0 represents prehypertension, the blood pressure being at normal levels (below 140 and 90 mm.) except under stress.

ion or slight elevation of nonprotein nitrogen in blood (up to 30 mg. per cent; upper limit of normal by method 25 mg.). Ocular fundi, grade IV.

In order to assess the results of treatment, we have set up arbitrarily certain rather rigid therapeutic grades, into which each patient was placed according to the findings during the latest month of therapy at the time of writing. These grades were chosen in order to provide an index of the prevailing level of blood pressure; the task of calculating average levels for each patient based on five readings a day for even one month's time is enormous and unrewarding, as fluctuations usually occur daily. We consider the grading of prevailing levels more indicative of the results of therapy than a consideration of the average reduction of pressure. Only in the case of patients show-

TABLE 1.—*Effects of Hyphex on Blood Pressure, All Cases, 6 to 25 Months*

Therapeutic Grade	Male					Female					Total
	4	3	2	1	0	4	3	2	1	0	
Initial Stage of Hypertension											
White Living											
IVc		5	5				3	6	1	1	21
IVb			4	3	1		4	2	2		16
IVa		1	4	2			4	7	2		20
III		11	29	11	1		15	39	16	2	124
II			4	3	1			9	1	3	21
Subtotal	0	17	46	19	3		23	63	22	6	202
White Dead											
IVc		2	3	1		1	2	3	2		14
IVb			2	1						1	4
IVa						2					2
III		1	1							1	3
II				1							1
Subtotal	0	3	6	3	0	3	2	3	2	2	24
Negro Living											
IVc			1								1
IVb		1						1		2	4
IVa			1								1
III			1	1			3	2	1		8
II									1		1
Subtotal	0	1	3	1	0	0	3	3	2	2	15
Negro Dead											
IVc		2				1	2	2			7
IVb							2	1			3
IVa		1									1
III								1			1
II											
Subtotal	0	3	0	0	0	1	4	4	0	0	12
Total	0	24	55	23	3	4	35	73	26	10	253*

* Plus 5 cases of terminal uremia not included in this table.
Grade 3 was deliberately chosen in 18 cases to avoid hypotensive episodes.

IV*c*. *Decompensated Malignant Hypertension.* Nitrogen retention present. Systolic pressure 200 to 300 mm. Hg; diastolic 130 to 220 mm. unless congestive heart failure is present. Ocular fundi, grade IV.

Certain patients with primary renal disease and renal insufficiency did not fit into these categories; the degree and severity of the hypertension was then estimated, neglecting the renal findings.

ing partial resistance will the latter method be used.

The various therapeutic grades are as follows:

0. Blood pressure always normal, systolic 140 mm. Hg or below, diastolic 90 or below.

1. Normal level of blood pressure 80 per cent of time; systolic never over 160 mm., diastolic never over 100 mm.

2. Reasonable levels of blood pressure. Systolic 160 mm. or below 80 per cent of time, never over 180 mm.; diastolic 95 mm. or below 80 per cent of time, never over 110 mm.

TABLE 2.—*Lowering of Average Diastolic Pressure in Patients Considered Partly "Resistant" to Hyphex (Therapeutic Grades 3 and 4)**

Diastolic pressure continuously reduced by:	Adequately Treated		Inadequately Treated†		Total
	Living	Dead	Living	Dead	
10–20 mm. Hg	4		9		13
21–30 mm.	13	1	4	1	19
31–40 mm.	9	5		2	16
41–60 mm.	1	1			2
>60 mm.				4	4
Total	27	7	13	7	54

* Excluding five patients upon whom lumbodorsal sympathectomy was performed 3 to 6 years previously and in whom severe hypertension recurred.

† Inadequate for one of the following reasons: Poor cooperation, intermittent cooperation, the presence of renal insufficiency, cerebral vascular disease or severe generalized atherosclerosis for which treatment was given cautiously.

3. Moderately hypertensive levels of blood pressure. Systolic 180 or below 80 per cent of time, never over 200 mm.; diastolic 100 or below 80 per cent of time, never over 120 mm.

4. Consistently hypertensive levels of blood pressure. Systolic 200 mm. or below 80 per cent of time, never over 220; diastolic 120 or below 80 per cent of time, never over 130.

The therapeutic responses of all cases could be included in these groups.

RESULTS

In all cases adequately treated blood pressure was considerably lowered. When the diastolic pressure had been elevated to levels of 140 to 160 or more, the systolic pressure was usually reduced to levels below that point and so maintained. Mishandling of cases by modification of the method and by omission of the drugs for variable periods of time gave rise to uniformly poor results.

In table 1 are the gross effects on blood pressure in all cases, both continuing and discontinuing therapy. The initial stages of the disease and the therapeutic levels of blood pressure sustained are shown. The malignant stage reversed itself in all cases adequately treated. No striking difference in responses of men and women was noticed. On the whole, Negro patients did badly. Of 77 white patients in malignant stages, 78 per cent attained good control of blood pressure and 54 have returned to full-time activity. Eighty per cent of 85 living white males were able to maintain their blood pressures at levels considered reasonable or lower (grades 2, 1, 0); 79 per cent of 117 white females were in similar categories. Therefore, in 80 per cent of all cases the blood pressure was controlled at levels of 160 mm. systolic or below most of the time and never exceeded 180 mm. The addition to these statistics of patients dying of various causes alters the results but little. The effects, however, were not as consistent in patients who were uncooperative or irregularly cooperative.

The reduction of blood pressure in the 20 per cent of cases partly resistant to the drugs is shown in table 2. But for four, the average change of diastolic pressure was greater than 20 mm. Hg. When readmitted to the hospital, all became normotensive at rest. Only one of these four had been in malignant stages; the rest were males with moderate or severe benign hypertension and atherosclerosis.

In a total of 18 patients exhibiting serious secondary complications, such as atherosclerotic cerebral vascular disease or renal insufficiency, the blood pressure was deliberately maintained at high (grade 3) levels; in five of 20 previously subjected to lumbodorsal sympathectomy it was necessary to lower the blood pressure only moderately in the supine position in order that severe postural hypotension would be prevented. Many partly "resistant" have altered with time; for example, during

the three months between February and May 1953, 14 classified as grade 3 have changed to grade 2 or better, while none in grade 2 or 1 has changed to grade 3. In 10 patients treated with 1-hydrazinophthalazine alone for various reasons, all but four with mild or moderate hypertension have been classified as achieving therapeutic responses of only grade 3 or 4. Likewise three in stage II given hexamethonium chloride only have been able to control their blood pressure at grade 3 levels.

The causes of death in both treated and discontinued cases is shown in table 3. In 9 of 43, renal insufficiency present before treatment progressed to uremia and death; five were in terminal stages of uremia. Therefore, the survival rate was relatively low in this group. Twenty-two have continued treatment and survived, four discontinued it and died, while six died of causes apparently unrelated to hypertension or renal insufficiency. When the nonprotein nitrogen in the blood was between 30 and 50 mg. per 100 cc. (normal 25 mg. per 100 cc.) treatment appeared to reduce it or leave it unchanged; when over 60 mg. renal insufficiency usually but not always progressed. The five patients dying during the initial hospital admission were all uremic. Excluding

TABLE 3.—*Cause of Death in Patients Both Receiving Hyphex and in Whom It Was Discontinued*

Cause of Death (Hypertensive Complications)	On Hyphex (223 Cases)				Total	Hyphex Discontinued (35 Cases)*				Total
	During Initial Hospital Admission		Later			During Initial Hospital Admission		Later		
	White	Negro	White	Negro		White	Negro	White	Negro	
Congestive Heart Failure					0			1		1
Coronary Occlusion			1		1			1		1
Cerebral Vascular Accident			2		2			3	1	4
Cerebral Edema					0			1		1
Renal Insufficiency, Developing					0		2	2		4
Renal Insufficiency, Previously present and moderate or marked	5		3‡	1	9	1	3			4
Subtotal, Hypertensive	5		6	1	12	1	5	8	1	15†
Interstitial Pneumonia			1	4	5					
Pneumonia			1		1					
Postoperative Shock				1	1					
Unknown but Normotensive			3		3					
Subtotal, Other			5	5	10					0
Total	5		11	6	22	1	5	8	1	15

Summary:		
Patients in Malignant (IV) Stages	10	13
Died of Acute Hypertensive Complications	3	10
Died of Progressive Renal Insufficiency	9	5
Died of Interstitial Pneumonia	5	
Died of Other and Unknown Conditions	5	
Living	201	20
Gross Mortality, per cent	9.9	43.0
Excluding Previous Renal Insufficiency	6.1	35.6
White Only, Excluding Previous Renal Insufficiency	4.2	27.6

* Discontinued for the following reasons: Lack of patient cooperation, 19; discontinued by physician, 11; drug fever, 2; became normotensive without drugs, 3.

† Eleven died soon after Hyphex was discontinued.

‡ Two patients died shortly after hexamethonium was discontinued.

renal insufficiency, only three patients died of the usual complications of hypertension while on treatment, and in no case did renal insufficiency develop. On the other hand, cessation of therapy in patients with malignant hypertension was invariably followed by death of hypertensive complications within 2 to 20 days (11 cases). Of the 10 dying of nonhypertensive causes, the lungs of five (four Negro and one white) exhibited interstitial pneumonia at autopsy.[5] The gross mortality in treated patients was 9.9 per cent; of those treated for a while only, 43 per cent. Analysis of the deaths among treated patients revealed that the malignant stage was present in all but two, both of whom exhibited severe atherosclerosis; among those in whom treatment was stopped, four were in benign stages. Therefore, it appears that moderately severe renal insufficiency is a limiting factor in the effectiveness of the method in many, but not in all cases, and that the prognosis in the malignant stage, while very much better than when untreated, is still poor for Negroes and for about one-fourth of white individuals. Excluding renal insufficiency, however, it is fairly good, only one-seventh dying of various other diseases.

Discussion

It is obvious that the use of both of these drugs together results in sustained lowering of the elevated blood pressure of hypertensive individuals. No case adequately managed has failed to respond. Once the response has occurred, it is maintained, unless dosage is reduced or omitted. Experience has shown a consistent relationship between level of dosage and response. Tolerance has not occurred when the regimen was strictly followed by the patient; in fact, it has been possible in many cases to reduce the dose substantially after a year or more.

Strict adherence to the regimen is, however, essential for successful control. Modifications of the schedule have caused failures. It is necessary that a constant blood level of both hexamethonium ion and 1-hydrazinophthalazine be present for blood pressure to be controlled and that "escape" resulting from discontinuation be prevented. By constant attention to bowels and by eliminating or reducing the dose of hexamethonium chloride according to the prevailing level of blood pressure, accumulation of excessive amounts and reactions thereto have been avoided; the oral form of the drug has been safely used for long periods of time by observing these precautions.

Substitution of placebos for one of the drugs was invariably followed by a progressive rise in blood pressure. When treatment had been continued for a few weeks, the rise usually occurred within 12 hours; after a year or more the rise sometimes appeared only after several days. Since the patient was aware of the change, controlled studies of this nature were difficult to make for more than a few days. Patients in malignant stages sometimes died within two to four days after discontinuing Hyphex; therefore administration of placebos was considered too hazardous to attempt. Two patients with renal insufficiency had shown no signs of progression for 8 and 10 months; discontinuation of hexamethonium chloride was followed within a month by death from uremia.

Signs of the malignant stage of hypertension disappeared completely in the 63 patients surviving, with none showing evidence of severe hypertension or retinopathy and with renal function often returning toward or to normal levels. The most severe test which we have been able to devise was given the method, no patient being refused treatment because of severity of the disease. No other therapy was given. The expected mortality in malignant hypertension treated by conventional methods for one year is high.[12] The seriousness of the disease present in this group of patients becomes manifest when each is graded according to the criteria of Smithwick[13] which take into account secondary conditions due to atherosclerosis as well as cardiac and renal degeneration. All patients in stages IV and III were in Smithwick's groups 4 and 3. Of those in stage II, 20 were in group 3 and 2 in group 2. The mortality rates in patients treated medically in one year according to Smithwick are: group 4, 50.5 per cent; group 3, 17.2 per cent; group 2, 9.6 per cent. For surgically treated patients (lumbodorsal sympathectomy) they are: group

4, 23.6 per cent; group 3, 4.6 per cent; group 2, 3.3 per cent. Therefore mortality rate in the present series of patients in his groups 4 and 3 treated by Hyphex up to two years is considerably lower than that of surgically treated patients, being 10.6 per cent for all causes of death, 5.8 per cent for those due to hypertension and uremia and 1.4 per cent for those due to hypertension without prior uremia.

Whether or not the course of benign hypertension is altered by control of the blood pressure will not be known until many years have elapsed. Experience has suggested, however, that some of the secondary effects of arterial hypertension may be prevented or postponed while others may not. For example, only two deaths from cerebral vascular accident have occurred, although 35 individuals had suffered one or more apoplectic strokes. No case of congestive heart failure has developed, nor has renal insufficiency appeared. From these relatively small numbers, we believe that cerebral arterial thrombosis may not be prevented, that renal insufficiency already present is often relatively intractable to treatment, but that cerebral hemorrhage, congestive heart failure, coronary occlusion and progressive renal damage may be postponed or prevented by control of the blood pressure. The basis for these beliefs will be presented in a subsequent communication. If an attempt to estimate the *stage* of hypertension now present in all individuals under adequate treatment were justifiable, 21 per cent would be in stage II (moderate benign), 53 per cent would be in stage I (mild benign), 21 per cent would be in stage 0 (prehypertensive), and 5 per cent would be normotensive. From another viewpoint, in every case the initial stage of the disease has regressed toward less severe ones, and in only 21 per cent (of stages II and III) has it failed to regress two or more stages.

It has been difficult to evaluate the results in this series of patients, which increased at the rate of about 12 a month, from the standpoint of duration of treatment. Over half have been taking Hyphex for a year or longer; they represent on the whole the more severe stages of the disease and its complications. In our experience, however, once control has been established for two or three months, it continues unless doses are altered or the patient fails to cooperate. Therefore, for the short term (25 months), tolerance to the drugs does not develop and progression of the primary disease is not to be expected unless renal insufficiency was present before treatment.

The method is by no means ideal. It represents a first approximation demonstrating that control is practical and feasible. Its hazards, both early and later, are discussed in the accompanying communication.[5]

Summary and Conclusions

A method for the control of arterial hypertension has been developed and used for 6 to 25 months in 258 patients of whom 89 were in malignant, 5 in terminal uremic, and 130 in severe benign stages. Blood pressure fell in all cases and was maintained at reasonable levels in about 80 per cent. Tolerance did not develop when the method was strictly followed. The malignant stage was altered in all cases, but only three-fourths survived. The limiting factor of effectiveness appears to be in cases of renal insufficiency. Negroes on the whole did poorly. The method is practical for patients desirous of cooperating, when certain precautions are taken to prevent hypotension and obstipation.

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Sumario Español

Este informe es el primero de una serie sobre el método de tratamiento de la hipertensión con cloruro de hexamethonium y hydrazinophthalazine. Cuando las drogas se tomaron estrictamente, la presión arterial se mantuvo a un nivel razonable o normal en 80 por ciento de

258 casos de hipertensión severa. El estado maligno cuando presente, fue reversado. La insuficiencia renal y ateroesclerosis cerebral severa limitan la efectividad de este método de tratamiento para la prolongación de vida.

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Demonstration of Differential Effects on Pulmonary and Systemic Arterial Pressure by Variation in Oxygen Content of Inspired Air in Patients with Patent Ductus Arteriosus and Pulmonary Hypertension

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Seven cases of patent ductus arteriosus with pulmonary hypertension and reversal of the usual direction of flow are described. Breathing of a low oxygen mixture either initiated or increased the reversed shunt, and breathing 100 per cent oxygen produced the reverse effect. Differences in oxygen saturation and dye-dilution curves recorded simultaneously from the radial and femoral arteries have allowed calculation of differences in the proportion of shunted blood flowing in these arteries and demonstrate that retrograde movement of blood in the aortic arch may occur.

IT HAS BEEN reported from this clinic[1, 2] and by others[3-11] that a patent ductus arteriosus may be associated with severe pulmonary hypertension and that, as a consequence, a reversal of the arteriovenous shunt usual in this condition may occur. The reversal of flow may be intermittent, or if permanent, a characteristic clinical picture of cyanosis of the feet with slight or absent cyanosis of the hands and face may be observed. Also, because the left subclavian artery is anatomically sometimes nearly opposite the aortic aperture of the ductus, the left hand may be cyanotic while the right is not. The general arrangement of the origins of the major arteries from the aortic arch are illustrated in figure 1, from which it may be deduced that a principal effect of the flow of venous blood from the pulmonary artery to the aorta would be a decrease in the oxygen saturation of the blood passing to the lower part of the body by way of the descending aorta, while the blood passing to the upper part of the body would be affected to a lesser extent or not at all.

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In 1946, von Euler and Liljestrand[12] found that in the cat the blood pressure in the pulmonary artery was increased when the animal breathed mixtures low in oxygen content, and similar findings have been reported in man.[13] These reports suggested to us an investigation of the effect of breathing varied oxygen mixtures on the degree of venous shunt in cases of congenital cyanotic heart disease,[14] and of the quantitative effect of such mixtures on the shunt from the aorta to the pulmonary artery in cases of patent ductus arteriosus associated with pulmonary hypertension.[15] It was suggested that the effects of breathing differing oxygen mixtures, including 100 per cent oxygen, might be of diagnostic value in some cases of patent ductus arteriosus with transient reversal of the shunt.

This communication presents data on seven patients with patent ductus arteriosus and pulmonary hypertension in whom either (1) the breathing of 100 per cent oxygen caused a disappearance or decrease in flow from the pulmonary artery to the aorta or (2) the breathing of a low oxygen mixture either caused the appearance of a flow, or accentuated the flow already present, in this direction.

Method

Cardiac catheterization was carried out on each patient utilizing a photokymographic recording assembly and associated equipment described elsewhere.[16, 17] Blood oxygen content, blood pressures and arterial dilution curves of T-1824 were recorded simultaneously from the radial and femoral arteries.[18-20] Oxygen saturation was determined both by manometric[21] and by photoelectric[22] technics. Estimation of venous-arterial shunts from dye-dilution curves was carried out as described elsewhere.[23, 24]

Table 1.—*Cardiac Catheterization Data From Patients With Patent Ductus Arteriosus and Pulmonary Hypertension*

Case	Right atrium	Right ventricle		Pulmonary artery		Right radial artery	
	Oxygen saturation, per cent	Oxygen saturation, per cent	Pressure, mm. of Hg	Oxygen saturation, per cent	Pressure, mm. of Hg	Oxygen saturation, per cent	Pressure, mm. of Hg
1	72	69	77/0	78	72/46	93	96/61
2	65	65	88/7	76	84/47	93	90/60
3	51	50	94/15	69	100/70	95	114/68
4	50	53	104/5	56	104/56	—	—
5	47	43	152/5	43	150/80	67	110/80
6	54	56	126/12	64	131/85	97	123/80
7	63	66	135/7	68	143/78	93	134/66

Clinical Data

None of the patients had a typical loud continuous murmur, four had a systolic murmur at the base, and two of the adults had a prolonged basal diastolic murmur. Apart from case 1, in which it was thought both preoperatively and postoperatively that the patient had a subaortic stenosis, it was believed that no complicating congenital defects were present. All the patients represented complex diagnostic problems, and in every instance the diagnosis was assured only after cardiac catheterization and studies of the oxygen saturation of the blood from the radial and femoral arteries. Six patients underwent surgical exploration. Two of the patients died following surgical closure of the ductus and in these no associated defect was found post mortem.

Case 1. The patient, aged 3½ years, first registered at the Mayo Clinic in October, 1950. The birth was normal but at 6 months of age a roentgenogram showed cardiac enlargement, and the home-town physician stated that there was a congenital heart defect with pulmonary congestion. At 2 years of age, the patient was in the hospital for two weeks with pneumonia. On our examination there was a loud basal systolic murmur. The heart was enlarged roentgenographically, and the electrocardiogram was interpreted as indicative of left ventricular hypertrophy. Catheterization was carried out under anesthesia, and the data indicated the presence of a patent ductus arteriosus (table 1). Surgical exploration was carried out on October 24; the heart was found to be very large and the pulmonary artery large and tense. A large patent ductus was present, being more than a centimeter in diameter, which was successfully closed by multiple ligation. The postoperative course was satisfactory. After operation a harsh short systolic murmur over the precordium persisted, and it was suspected, as before operation, that there was an associated subaortic stenosis. The patient returned for examination in August, 1951, at which time there was a thrill in the suprasternal notch and a grade 2 systolic murmur in the aortic area. The heart had decreased markedly in size on roentgenologic study and the vascularity of the lung was less notable than on preoperative study. The general condition was very satisfactory.

Case 2. A boy, aged 5 years, was brought to the clinic in August, 1951, for evaluation of his heart disease. He had been admitted to the clinic previously at the age of 10 months for treatment of an acute bronchitis, at which time a loud rough systolic murmur had been noted in the midsternal area. On the occasion of the second admission there was a grade 2 systolic murmur maximal in the second and third intercostal spaces and well transmitted toward the left clavicle and back. The blood pressure was 92 mm. Hg systolic and 60 mm. diastolic. The heart was moderately enlarged roentgenologically and the pulmonary vascular shadows were increased. The electrocardiogram was interpreted as indicative of biventricular hypertrophy. The diagnosis of patent ductus arteriosus was confirmed by cardiac catheterization (table 1), the catheter passing through the

ductus. Following successful surgical closure of the ductus, no murmurs were present and convalescence was uneventful.

Biopsy of the lung disclosed increased thickness of the media and prominence of the internal elastic lamina of the small pulmonary arteries, but these arteries were free of intimal disease. The walls of the arterioles were of increased thickness with an increased degree of cellular structure, but the difference from normal could be graded only mild to moderate.

Case 3. The patient was first seen at the clinic in November, 1950, at the age of 21 years, when he was admitted to the hospital with heart failure. A heart murmur was said to have been noted at birth, and during his childhood he had been restricted in his activities. In 1946, while suffering from an upper respiratory infection, he was said to have been bluish in color. In October, 1949, there had been swelling of the abdomen and discomfort in the right upper quadrant. The legs and ankles became swollen, and paracentesis had been carried out 22 times in the year prior to November, 1950.

Our examination disclosed a loud rough apical systolic murmur and thrill, and a short early diastolic murmur at the apex and xiphoid area. The clinical findings indicated marked right ventricular hypertrophy and pulmonary hypertension. No definite cyanosis could be recognized. Clinically, the most likely diagnosis was thought to be a ventricular septal defect with aortic insufficiency. It was believed that tricuspid insufficiency might be an associated condition. A roentgenogram showed marked cardiac enlargement with prominence of the left border. The electrocardiogram (fig. 2, case 3) showed an intraventricular conduction disturbance, the QRS measuring 0.10 second, and was characterized by right axis deviation, a high wide R in V_1 and a triphasic QRS in V_6. In a V_R, not illustrated, Q and R deflections were of approximately equal amplitude.

Following catheterization studies during which the aorta was entered through a ductus, exploratory thoracotomy was carried out on November 7. A large patent ductus was found and ligated, although at the time of exploration the heart dilated and slowed and it was necessary to resort to cardiac massage for a time to maintain cardiac function. The postoperative convalescence was satisfactory.

The patient returned 10 months later, in September, 1951, stating that he was able to do his farm work but had slight dyspnea if he overworked. There had been no swelling of the feet but there had been occasional soreness in the hepatic region. He had not required any further paracentesis. He had discontinued use of digitalis in May and had had recurrence of mild symptoms, requiring treatment with mercurial diuretics and resumption of his use of digitalis. At the time of re-examination he had remarkably good exercise tolerance. There was a grade 2 apical systolic murmur. The preoperative pressure in the pulmonary artery had averaged 100 systolic and 70 diastolic. Catheterization on Sept. 11, 1951, 10 months after operation, revealed a pulmonary pressure that averaged 55 systolic and 22 diastolic; the pressure in the right ventricle was 54/0.

Case 4. The patient was first admitted at the age of 24 years, on Aug. 19, 1952, because of pregnancy. A heart murmur was known to have been present since the age of 3, and some cyanosis of the feet had been noticed since the age of 13. During the school years it was said that she was moderately dyspneic on effort. She carried her baby to term satisfactorily and was delivered of a live baby, low forceps being used, on October 16. There was blood in the amniotic fluid and the placenta showed evidence of a recent premature separation. The day following delivery she complained of increased dyspnea and palpitation and noted deeper cyanosis of the nails. On October 22 there was repeated hemoptysis. She was dismissed from the hospital on November 2, and returned for further investigation six weeks later. The main auscultatory finding was a grade 3 diastolic murmur that was maximal in the left infraclavicular area. A short systolic murmur was also present in the pulmonary area. The second sound in the pulmonary area was moderately accentuated. Roentgenograms showed that the size of the heart was within normal range in the anteroposterior view, but there was marked prominence of the pulmonary artery. In the oblique roentgenograms there was evidence of right ventricular hypertrophy. The electrocardiogram was interpreted as indicative of right ventricular hypertrophy (fig. 2, case 4). Surgical exploration was carried out on January 10, and a huge patent ductus, exceeding the size of the aorta, was successfully divided and its ends sutured. About two hours after the completion of the operation, marked hypotension developed without any prior warning symptoms, and death occurred in about 20 minutes.

The postmortem examination did not reveal any specific reason for the death. The heart showed no complicating defect. The right ventricle (fig. 1*c*) was thick, being approximately equal to the thickness of the left ventricle, which was of normal size. The large pulmonary arteries were unobstructed; the small arteries had a varied structure, some appearing to be dilated, others moderately thick-walled, and still others occluded by intimal changes.

Case 5. The patient was first registered at the clinic in 1939 at the age of 18 years, at which time a diagnosis of severe scoliosis and patent ductus arteriosus was made. A "machinery" murmur was noted by the consultant. The patient returned in 1942 for a re-evaluation of the scoliosis and the cardiac condition; at that time she was noted to

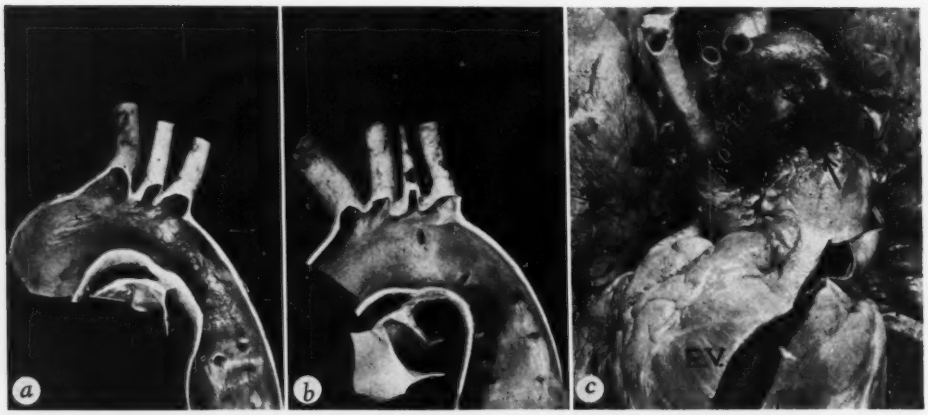

FIG. 1(*a* and *b*). Two normal aortas from which the anterior half of the wall has been removed to demonstrate the relationship of the aortic arch vessels to the ligament of the ductus arteriosus. While the ligament is distal to these branches, it is more definitely so in *a* than in *b*. In the latter it may be noted that the left vertebral artery arises as a separate branch of the aorta, a not uncommon arrangement. It is to be emphasized that considerable variation in the arrangement of the origin of these vessels occurs. (*c*) The great vessels in case 4. The divided and sutured ends of the ductus are indicated by the arrows. The hypertrophy of the right ventricle (R. V.) is evident. It is of interest that blood shunted through the ductus could be detected in the right radial artery in this case (fig. 5). (These photographs of specimens are used through the kindness of Dr. J. E. Edwards, Section of Pathologic Anatomy, Mayo Clinic.)

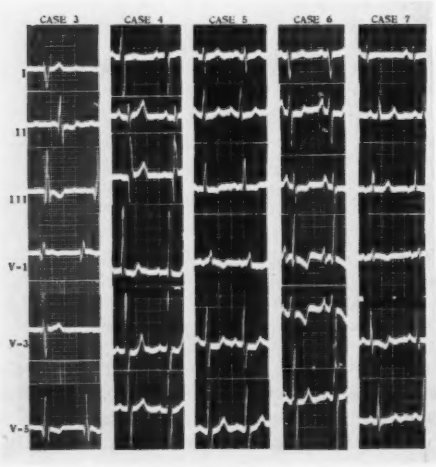

FIG. 2. Electrocardiograms from five adult patients with patent ductus arteriosus and pulmonary hypertension. These tracings were taken during the admission during which cardiac catheterization was performed.

have adequate cardiac reserve, and it was thought best to defer surgical treatment. On her return in November, 1951, the cardiac status had worsened considerably, the patient being much more disabled. She gave a history of having had, in November and December, a prolonged illness called "septicemia" which was treated with penicillin and streptomycin for seven weeks. It was apparently believed that she had had a subacute bacterial endocarditis or endarteritis. The possibility of thyrotoxicosis also had been suggested, but the clinical evaluation supported by radioiodine studies indicated that she was euthyroid. The auscultatory findings were a grade 3 systolic murmur and thrill in the third left intercostal space with a grade 1 continuous murmur to the left of the sternum. An interesting phenomenon was observed in that following her occasional extrasystoles, there was the occurrence of a marked, prolonged diastolic murmur and accentuated pulmonic second sound. The problem of surgical therapy again arose, and at that time (November, 1951) it was believed that, in spite of the severe scoliosis, such treatment might be carried out safely and perhaps with benefit. When the patient returned on her last visit in August, 1952, her condition had further deteriorated. The feet were slightly cyanosed when the hands were not. The heart was enlarged, but its size was difficult to assess because of the kyphoscoliotic deformity. The vital capacity was 860 cc. The electrocardiogram showed right axis deviation and evidence of right ventricular hypertrophy (fig. 2,

case 5). Cardiac catheterization was carried out (table 1) to determine pulmonary arterial pressure, which was found to exceed the systemic pressure. It was the final opinion that surgical treatment could not then be recommended.

Case 6. The patient first registered at the clinic in January, 1950, at the age of 35. He reported that at the time of birth the physician had said that he had a weak heart. His development was normal and he engaged in routine athletic activities during his school years. He considered himself in good health until 1945, when he began to notice orthopnea and was hospitalized and given digitalis and mercurial diuretics. He got along relatively well on a program of restricted activity until January, 1949, when there was an increase in dyspnea, but improvement occurred with restriction in his activities. In April, 1949, he had further exacerbation of the dyspnea, and edema of the legs developed. He was admitted to the hospital, and improvement occurred with loss of the edema. His condition had been relatively unchanged until his admission here.

On examination, his weight was 143 pounds, and his blood pressure was 150 systolic and 90 diastolic. A long loud diastolic murmur was present in the second and third left intercostal spaces and this was well heard also at the apex. Roentgenographically, the heart was huge and there was prominence of the pulmonary artery and vascular shadows. The electrocardiogram (fig. 2, case 6) showed right axis deviation and evidence of right ventricular hypertrophy in the precordial leads. The final clinical assessment was that a severe pulmonary hypertension and right ventricular hypertrophy related to congenital cardiac disease were present. Cardiac catheterization (table 1) proved the presence of a ductus.

Surgical treatment was carried out on March 11, 1950. The pulmonary artery was found to be extremely large and sclerotic. The ductus was approximately 2.5 cm. in diameter and very short. It was impossible to use transfixion sutures, but two braided silk ligatures were passed around the ductus and tied down as tightly as was thought reasonable with regard to the structural changes in the ductus and pulmonary artery. The patient's condition was critical throughout the operation and his postoperative course was stormy. A prolonged basal diastolic murmur was still present at the time of his dismissal. The question was raised at this time whether the ductus would remain closed.

The patient returned for re-examination in October, 1950. He had continued to have chronic congestive failure without much change in the general picture. Cardiac catheterization was carried out again and the ductus demonstrated to be open. When the patient returned in January, 1952, his general condition appeared somewhat better and he had been able to get along satisfactorily without mercurial diuretics, but with digitalis medication and sodium restriction. The results of cardiac examination were as before.

Case 7. The patient was first seen at the age of 45, in August, 1952, with the complaint of shortness of breath for many years and "constant cold" of four years' duration. A cardiac murmur was said to have been first discovered at the age of 10. For many years the patient had continued to work as a clerk for eight hours daily. There had been no orthopnea, and there had been no recent progression of symptoms. Her weight was 130 pounds and her blood pressure was 130 systolic and 80 diastolic. There was a prolonged grade 2 plus diastolic murmur that was maximal to the left of the sternum from the fifth rib to the left infraclavicular area. The pulmonic second sound was accentuated. No systolic murmur was heard. The roentgenogram showed marked prominence of the pulmonary artery segment and the pulmonary vessels. The electrocardiogram (fig. 2, case 7) was interpreted as presenting evidence of biventricular hypertrophy, showing an "M" QRS complex in V_1 and a high R and small S in V_5. At cardiac catheterization the presence of a patent ductus arteriosus was established.

Surgical exploration was carried out on September 10 and an aneurysmal dilatation of the pulmonary artery was found. The patent ductus arteriosus was of about the same diameter as the aorta and was approximately 1 cm. in length. It was possible to divide the ductus and suture its ends. The patient's immediate postoperative course was satisfactory. There was persistence of a diastolic murmur to the left of the sternum. On the seventh postoperative day there were two episodes of pain in the right shoulder and slight dyspnea, and a few hours later severe dyspnea with cyanosis, shock and death.

Postmortem examination showed the sutured ends of the ductus to be in good condition, and the exact cause of death was not determined. The right ventricle was markedly thickened. No associated cardiac defect was present. The pulmonary vascular changes were not uniform, some vessels showing relatively minimal change, while others showed medial hypertrophy and intimal change of advanced degree. The histopathologic picture did not approach the severe degree that has been described in other cases of patent ductus arteriosus.[25]

Laboratory Data

The laboratory data on the seven patients are summarized in tables 1 and 2. In table 1 are given the more routine findings on cardiac catheterization, where it may be noted that in the group generally the pulmonary and systemic arterial pressures were nearly equiv-

alent, the exceptions being case 1, a young child, in which the pulmonary arterial pressure was significantly lower, and case 5, in which it was significantly higher than the systemic pressure. In cases 4, 5 and 7 there was insufficient arterialization of the blood in the pulmonary artery, so that from the routine data given in this table the diagnosis would not have been obvious during the catheterization procedure had not the catheter entered the aorta. In case 4 no data on the pressure or calculated across the ductus. The anatomic relationship of the ductus to the branches of the aortic arch (fig. 1) determines a preferential flow of blood from the ductus to the descending aorta. Hence the presence in the femoral artery of blood with an oxygen saturation significantly lower than that of a sample drawn simultaneously from the radial artery is positive evidence of a right-to-left shunt through a patent ductus arteriosus. Further evidence of the presence of this condition may

TABLE 2.—*Effect of Variation in the Oxygen Content of Inspired Air on Pulmonary and Systemic Arterial Pressures and on Differences in Oxygen Content of Simultaneously Withdrawn Radial and Femoral Arterial Blood (Patients With Patent Ductus Arteriosus and Pulmonary Hypertension)*

Case	100% Oxygen*					Room air*					Low oxygen mixture*				
	O_2 content vol. %		Pressure, mm. of Hg			O_2 content, vol. %		Pressure, mm. of Hg			O_2 content, vol. %		Pressure, mm. of Hg		
	Rad. art.	Fem. art.	PA or RV	Rad. art.	Fem. art.	Rad. art.	Fem. art.	PA or RV†	Rad. art	Fem. art.	Rad. art.	Fem. art.	PA or RV	Rad. art.	Fem. art.
‖1‡	15.7	16.1	67/42	92/54	96/48	13.4	13.5	83/58	96/51	108/58	2.8	1.3	63/47	56/32	64/31
2‡	18.9	18.6		88/47	83/43§	15.8	14.6	84/47	90/60	90/70§					
3	19.3	19.3	108/11†	107/64	125/56	16.8	16.7	106/12†	114/68	124/62	13.0	12.3	108/11	118/67	134/60
4	21.2	20.1		132/73	142/74	19.5	16.7		127/68	127/69	14.0	9.7		118/70	125/75
5	20.0	16.0	150/90	110/80	135/85	15.7	11.0	160/90	110/80	110/75	11.4	4.2	160/89	112/80	132/86
6	26.9	26.5	137/81	154/83	149/77	23.7	22.8	147/90	161/88	157/84	17.3	13.0	155/93	165/90	156/86
7	24.2	23.2	140/74	130/70	151/67	22.0	19.7	144/5†	143/66	134/66	17.1	15.0	145/80	145/71	157/71

* Gas mixture being breathed.
† Catheter in right ventricle.
‡ Avertin anesthesia.
§ Descending aorta.
‖ Pulse badly damped by clot in intra-arterial needle.
Abbreviations: PA, pulmonary artery; RV, right ventricle.
The low oxygen mixture differed for individual patients. Mixtures containing 10 to 14 per cent of oxygen in nitrogen were used.

oxygen saturation of the blood in the radial artery were obtained during catheterization.

In table 2 are shown data obtained during additional studies on the arterial pressure and oxygen saturation of blood withdrawn simultaneously from femoral and radial arteries while the patient breathed differing oxygen mixtures. The figures given in the two tables do not correspond exactly, as in some instances a second study was done on a different day. While the systolic systemic arterial pressures and the pulmonary arterial pressure, where recorded in table 2, were taken simultaneously, the former are not a sufficiently accurate reflection of the aortic pressure to allow instantaneous pressure gradients to be be derived from dye-dilution curves recorded following injection of Evans blue dye into the pulmonary artery via a cardiac catheter.[26]

Each case has features of special interest regarding the laboratory data. In case 1 catheterization was done under anesthesia, and after the diagnosis of arteriovenous shunt between the aorta and pulmonary artery was established, arterial needles were inserted into both the femoral and radial arteries in order to obtain arterial blood samples and hence to differentiate between a patent ductus arteriosus and an aortic-pulmonary fistula of the base of the great vessels. To increase the diagnostic potency of this test a mixture containing 10 per cent oxygen was also administered. The

esults gave confirmatory evidence to the liagnosis of patent ductus arteriosus, but the ypoxemia produced by 10 per cent oxygen vas more profound than was wished; it was hought possible that the lungs were practically xcluded from the circulation temporarily oward the end of the test period, the blood amples from the pulmonary and femoral

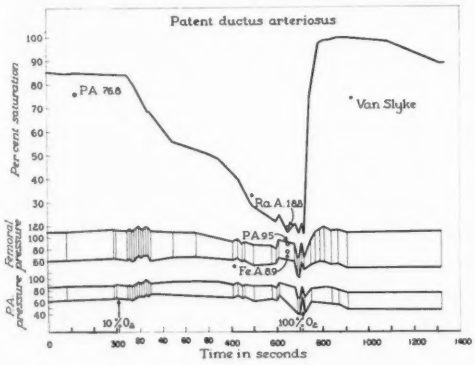

FIG. 3. Femoral and pulmonary arterial pressures, together with the ear oximeter values of the arterial saturation, in a patient with patent ductus arteriosus and pulmonary hypertension (case 1) during the breathing of 10 per cent oxygen. It was not appreciated at the time that the arterial oxygen saturation was dropping so precipitously. The inset values represent oxygen saturation; values marked with an asterisk were obtained by Van Slyke determinations, the others being obtained by a cuvette oximeter. Note the similarity in oxygen content of femoral and pulmonary arterial blood at the end of the period of hypoxia; this similarity presumably is a result of the increased rate of flow through the ductus from the pulmonary artery to the aorta. P. A., pulmonary artery; Ra. A., right radial artery; Fe. A., femoral artery. The expansion of the time scale on the chart during the first 100 seconds of breathing the low oxygen mixture is to be noted.

arteries having an extremely low oxygen content and the radial blood sample having only a slightly higher content (fig. 3). If the reversed shunt had taken place at the origin of the great vessels (aortic-pulmonary fistula), its effect on the blood in the vessels originating from the arch should have been approximately equal to the effect on the blood in the descending aorta. The possibility that left ventricular failure related to the concomitant subaortic stenosis could have occurred is to be considered, but there were no signs of pulmonary congestion or later untoward effects.

In case 2 the patient was also catheterized under anesthesia and the catheter entered the aorta through the ductus. The pressures and oxygen saturations at various sites of the catheter tip are shown in table 2 and figure 4. A difference between the oxygen content of the right radial artery and that of the descending aorta existed when the patient was breathing air, but this difference disappeared when he breathed 100 per cent ygen. No lowox oxygen mixture was administered to this patient.

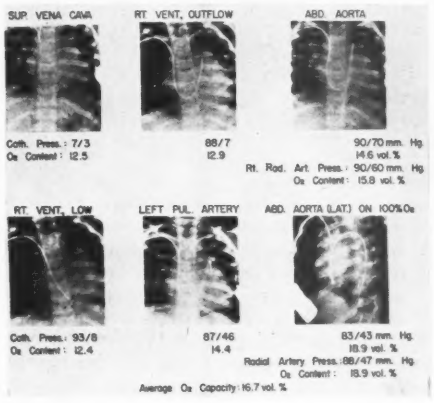

FIG. 4. Recorded pressures and oxygen saturations at various sites of the catheter tip in a patient with patent ductus arteriosus and pulmonary hypertension (case 2). The near identity of the pressures in the aortic, radial and pulmonary arteries is to be noted. When the patient was breathing air, there was a difference of 1.2 volumes per cent (upper right) between the oxygen content of blood samples withdrawn from the descending aorta and the content of those withdrawn from the right radial artery. This difference was abolished when the patient breathed 100 per cent oxygen (lower right).

In case 3 there was no difference between the oxygen content of the radial and femoral blood samples when the patient breathed 100 per cent oxygen or air, but there was a small though significant difference (0.7 volume per cent) when 12 per cent oxygen was breathed. The catheter was made to enter the aorta several times and the continuous record showed no readily demonstrable pressure

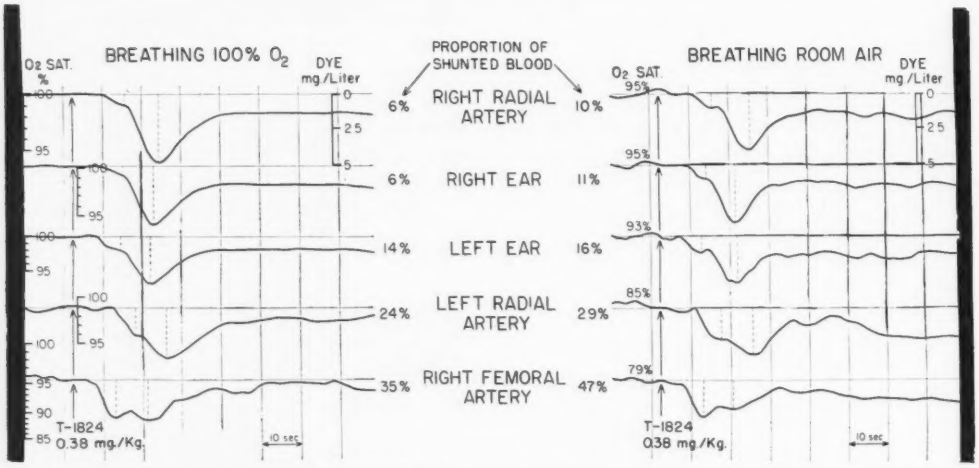

FIG. 5. Differences in dye-dilution curves obtained from multiple sites in the arterial system in a patient with patent ductus arteriosus and pulmonary hypertension (case 4). Five curves were recorded simultaneously while the patient breathed 100 per cent oxygen (left panel) and room air (right panel). The oxygen saturation scales on the left panel indicate the relative sensitivity of the oximeters; the numeral just above the start of each curve on the right panel represents the oxygen saturation of arterial blood at that particular site while the patient breathed room air. Note in each panel the increase in magnitude of the initial deflection (indicated by the first vertical broken line) relative to the main deflection (second broken line) as the sampling site is moved from the right radial artery to the femoral artery and that this difference is even greater when the patient is breathing room air than when she is breathing 100 per cent oxygen. The figures on each side of the central panel indicate the proportion of shunted blood appearing in each arterial site as calculated from the dilution curve.[17] Smaller fluctuations appearing in all curves of the right-hand panel and in the lower curve of the left panel are due to variations in arterial oxygen saturation attributable to phasic variations in the magnitude of the right-to-left shunt.

TABLE 3.—*Effect of Variation in the Oxygen Content of Inspired Air on Blood Oxygen Saturation at Various Sites in the Systemic Arterial System of a Patient with Patent Ductus Arteriosus and Pulmonary Hypertension**†

Site	Blood oxygen saturations when oxygen content of inspired air was			
	100%	20%	14%	10%
Right radial artery	100	95	86	69
Right ear	100	95	87	67
Left ear	100	93	77	62
Left radial artery	99	85	75	54
Right femoral artery	95	79	69	45

* Case 4. See text for details.

† Note increase in degree of desaturation at different arterial sites relative to their origin in the distal direction along the aortic arch.

difference on withdrawal until the right ventricular pressures were recorded. This was so, despite the fact that approximately 30 per cent of the left ventricular output was being shunted into the pulmonary artery via the ductus. The record showed some artefact related to catheter movement which, along with a cardiac irregularity, vitiated accurate measurements of pressure. Whether there was a persistence of the left-to-right shunt, as well as the slight reversal on the breathing of 12 per cent oxygen, is unknown, since during this period the catheter tip was in the right ventricle. It may be mentioned again that 10 months after surgical closure of the ductus the pulmonary arterial pressure was 55/22 and no shunt was demonstrable.

The cases are arranged in order of age, but actually case 4 was the one most recently studied. The early cyanosis of the feet in this case clinically suggested an associated coarctation of the aorta above the ductus. While the laboratory data would not necessarily exclude

such an associated defect, they were interpreted as favoring the absence of such a lesion; that is, the similarity in the radial and femoral pressures and the characteristic dye-injection studies to be described were so interpreted. Dye-concentration curves were obtained after the method of Nicholson and co-workers,[18] and the quantity of blood shunted was calculated on the basis of the ratio of the area of the primary deflection to the area of the secondary deflection after the method of Swan and co-workers.[24] The calculations of the shunt, expressed as the proportion of arterial flow composed of shunted blood, for the right radial, right ear, left ear, left radial and right femoral sites were: breathing 100 per cent oxygen, 6, 6, 14, 24 and 35 per cent, respectively; and breathing air, 10, 11, 16, 29 and 47 per cent, respectively (fig. 5). The per cent arterial oxygen saturation at various sites with the patient breathing various oxygen mixtures is given in table 3, which shows progressive desaturation from right to left in respect to the branches of the aortic arch. That a small venous shunt from the pulmonary artery via a ductus may affect the saturation in all vessels of the aortic arch is more readily and conclusively demonstrated by arterial dye-dilution curves than by the values for oxygen saturation of the blood samples.

In this patient (case 4), the fact that pulmonary arterial blood was reaching the innominate and right radial artery was clearly shown by the initial contour of the dye curve from the latter vessel when the values for oxygen saturation were inconclusive. The femoral arterial dye curve had the characteristic double-hump contour associated with a large venous shunt. Of further interest were the facts that the femoral and left radial oximetric records showed marked phasic variations related to the respiratory cycle, while the records from the two ear oximeters and right radial artery did not; and while no left-to-right shunt through the ductus was present when the patient breathed air, there was some evidence of it when she breathed 100 per cent oxygen, as ascertained by some arterialization of blood in the pulmonary artery. The arrangement of the aortic arch branches in this case are shown in figure 1.

Case 5 is of special interest in that the pulmonary arterial pressure grossly exceeded that in the systemic arteries. There had been marked recent increase in the disability, and how much of this might be attributed to concomitant pulmonary disease with the severe kyphoscoliosis was conjectural.

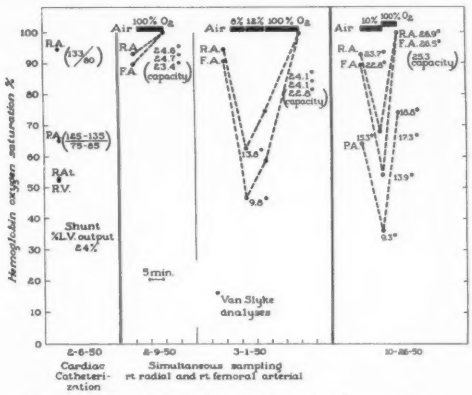

FIG. 6. The effect of variations in the oxygen content of inspired air on the oxygen content of blood samples simultaneously withdrawn from the radial and femoral arteries in a patient with patent ductus arteriosus and pulmonary hypertension (case 6, see text for details). Note that on three separate occasions a difference in arterial oxygen saturation existed between blood samples taken from the right radial artery and those taken from the femoral artery, and that this could be abolished by the breathing of 100 per cent oxygen. The difference in arterial oxygen saturation was accentuated on two occasions by the breathing of mixtures low in oxygen (8 to 12 per cent). The cardiac catheterization findings are given in the first column. R. A., right radial artery; P. A., pulmonary artery; R. At., right atrium; R. V., right ventricle; F. A., femoral artery.

Case 6 is one of the earliest cases studied, and data were collected both before and after surgical treatment, following which the ductus reopened. The studies on the oxygen saturation are summarized in figure 6. A reproduction of the simultaneous pressure records from the pulmonary, radial and femoral arteries obtained during the studies on Oct. 26, 1950, is seen in figure 7. The patient was again restudied in January, 1952, at which time there was a difference of 1.0 volume per cent in

oxygen saturation between the radial and femoral arterial samples while the patient was breathing air, but the values were similar for samples taken from the two arteries when the patient was breathing 100 per cent oxygen.

Dye-dilution curves were recorded from radial and femoral arteries and both ears a second deflection which corresponded in time and in contour to the curve seen when the patient breathed 100 per cent oxygen, except that the disappearance time was no longer disproportionately prolonged. These curves indicated that with 16 per cent oxygen a right-to-left shunt was occurring, while the left-to-

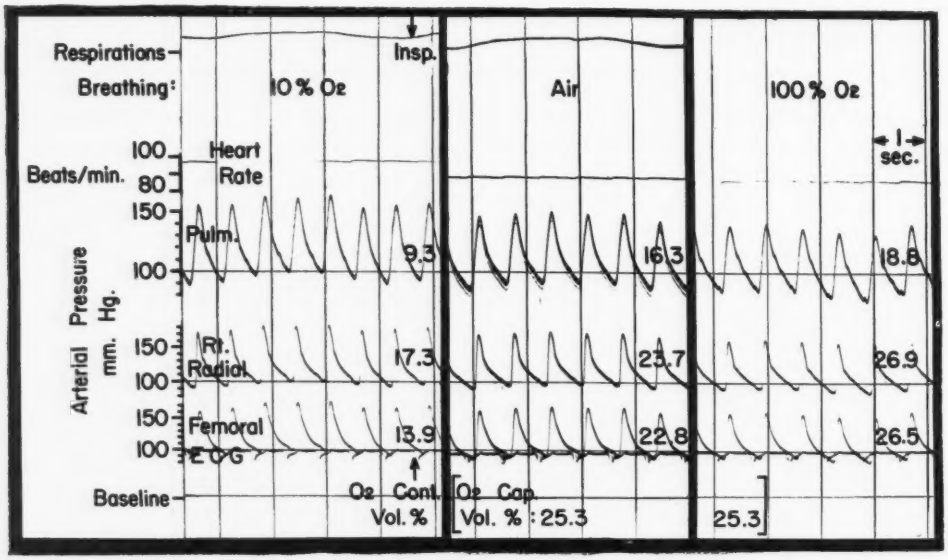

FIG. 7. Pulmonary and systemic arterial pressures and oxygen content of simultaneously withdrawn blood samples in a patient with patent ductus arteriosus and pulmonary hypertension (case 6) while differing oxygen mixtures were being breathed. Note the similarity in pressures and contours of all three pulses in the three states studied, and that the pulmonary pressure was relatively decreased when the patient breathed 100 per cent oxygen. Note also the resulting differences in oxygen content between simultaneously withdrawn radial and femoral arterial samples; these differences are greatest when the patient breathes 10 per cent oxygen, and are present to a progressively less degree when room air and 100 per cent oxygen are breathed. The proportion of shunted pulmonary arterial blood in the femoral arterial flow amounted to 42, 12 and 5 per cent, respectively, when the patient breathed 10, 21 and 100 per cent oxygen.

while the patient breathed 100 per cent oxygen and also 16 per cent oxygen. With 100 per cent oxygen the contours of the curves were similar for all four sites, but the time components were prolonged with a disproportionate increase in disappearance time indicative of a low cardiac output with pulmonary recirculation.[23] When the patient breathed 16 per cent oxygen, the contours for all sites were again similar but differed from the first series in the occurrence of a premature deflection that returned to the base line. This was followed by right shunt that was evident with 100 per cent oxygen was no longer present. When the proportion of shunted pulmonary arterial blood present at each site was calculated from the dilution curve,[17] it was found to be 13, 9, 15 and 34 per cent respectively in the right radial arterial, right ear, left ear and right femoral artery, indicating that under this circumstance a higher proportion of shunted blood was passing to the caudal than to the cephalic portion of the body.

In case 7, simultaneous dye-dilution curves

were recorded from the radial and femoral arteries while the patient breathed 100 per cent oxygen and air, with the dye injected via the catheter in the pulmonary trunk. In each instance, both the ear-piece curves and the

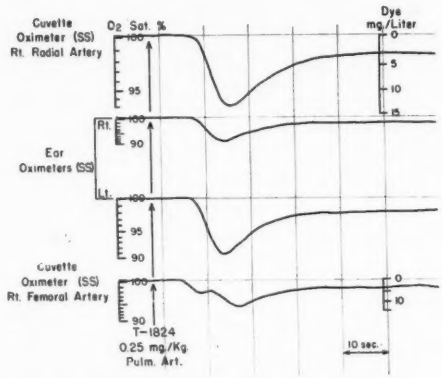

FIG. 8. Differences in dye-dilution curves recorded simultaneously from cephalic (radial artery and both ears) and caudal (femoral artery) sites in the arterial system of a patient with patent ductus arteriosus and pulmonary hypertension (case 7, see text for details). The patient was breathing 100 per cent oxygen. The comparative sensitivity of the different oximeters is shown by the oxygen saturation scale included for each oximeter. Except for differences in amplitude caused by variations in sensitivity, there is similarity in contour of the dilution curves recorded from the right and left ears and the right radial artery. The curve from the femoral artery was, however, significantly different from the other three, showing a shorter appearance time and an abnormal initial hump caused by dyed blood shunted via the ductus from the pulmonary artery to the descending aorta. Measurements on this curve indicate that approximately 20 per cent of the blood from the femoral artery had originated from a right-to-left shunt. The disappearance limbs of all four curves are prolonged to a degree compatible with a left-to-right shunt[18] (pulmonary recirculation) amounting to 20 per cent of the pulmonary arterial flow.

radial artery curve were within normal limits; however, the femoral dye-dilution curve showed a shortened appearance time with a double-hump contour on the build-up slope characteristic of a right-to-left shunt (fig. 8). Dye-dilution curves of this type from the femoral artery have also been noted by Bothwell and co-workers.[9]

COMMENT

As previously reported,[15] the production of change in magnitude or direction of flow through a patent ductus arteriosus by variation of the oxygen content of the inspired air is a unique and unequivocal method of demonstrating a differential effect of oxygen on the pulmonary and systemic circulations. It is generally conceded that pressure in the pulmonary artery usually varies inversely with the oxygen tension of the respired gas. However, the mechanism of, and lack of uniformity in, the pulmonary vascular response in man and animals have been controversial issues.[27] That the effect is mediated by the sympathetic nerves is indicated by the work of Stroud and Rahn,[28] who found in animals absence of the response in the sympathectomized lung. The absence of the pulmonary pressor effect in animals as noted by Beard and co-workers[29] when 8.5 per cent oxygen was breathed might in part be related to the narcotized state. The possibility that in our patients a rise in left atrial pressure could have contributed to a rise in pulmonary resistance cannot be excluded as a factor in the change on low oxygen breathing but does not find likely application in the explanation of the change related to the shift from air to 100 per cent oxygen or vice versa. The decrease in pulmonary arterial pressure on change from air to 100 per cent oxygen, illustrated in figure 7, was as clear-cut as the decrease on changing from 10 per cent oxygen to air. It is to be noted that frequently there was a bidirectional shunt through the ductus orifice. While this might be considered related in part to turbulence, it seems more likely related to variations in the direction of flow during the cardiac cycle. If the latter were true, a variation in heart rate, with change in the relative durations of systole and diastole, might cause a change in the magnitude of the shunt, but it is thought that such an effect, if it occurred, would be insignificant, as the changes in heart rate were minimal.

The fact that a venous-arterial shunt through a patent ductus affected the oxygen saturation of the blood in the aortic arch vessels that originate proximal to it, was noted in several

cases but particularly in case 5. This finding demonstrates retrograde movement of blood in the aorta probably in late systole or diastole. Whether this backflow occurs during closure of the semilunar valves at the end of systole or is due to phasic differences in ventricular ejection or capacity of the aorta and pulmonary artery to take up the stroke volume of the respective ventricles, or a high runoff from the proximal branches of the aortic arch, or to these and additional factors, is at present uncertain.

The phenomenon of reversal of the arteriovenous shunt in patent ductus arteriosus is not usual even when some degree of pulmonary hypertension is associated with the congenital lesion. Thus the over-all incidence of veno-arterial shunt in patent ductus arteriosus is small, and the cases which we have discussed are distinctively atypical on hemodynamic and clinical grounds. We have seen two cases of patent ductus in which the magnitude of the pulmonary arterial pressures as related to the systemic arterial pressure was within the range of that of the seven cases presented above, but in which the use of differing oxygen mixtures failed to influence the magnitude of a shunt already present.

Further emphasis may be placed on the fact that the patient with the syndrome of patent ductus arteriosus and severe pulmonary hypertension may have a clinical picture, that is, basal systolic murmur, enlarged heart and vascular shadows, and electrocardiographic findings, which might suggest Eisenmenger's complex. Indeed, if only a routine catheterization of the heart were done and single samples of blood from the various chambers were obtained, the diagnosis of Eisenmenger's complex might be thought to have been supported. When the catheter passes through the ductus, the diagnostic importance of which has been emphasized by Limón Lason and co-workers,[6] the problem is simplified but in the absence of such an event, comparison of the oxygen content of the blood in the radial with that in the femoral artery is a most important investigative procedure. It might be mentioned that the Eisenmenger complex in case 2 of Cosby and co-workers'[30] group of cases, as well as in such cases of our own, closely resembled the clinical complex of patent ductus and pulmonary hypertension with some reversal of flow through the ductus.

The problem of surgical exploration in adult cases of this type is a very difficult one, and the justification for exploration may be largely dependent on the fact that the immediate mortality is not prohibitive rather than on a real hope of "cure." Case 3 is of pertinent interest, as the heart failure seemed to have been alleviated and the pulmonary pressure was markedly reduced. Case 7 is of particular interest in that on postmortem examination the pulmonary vascular changes were not sufficiently extensive to make one believe that the pulmonary hypertension was necessarily irreversible. When this patient breathed 100 per cent oxygen there had been evidence of a shunt in the aortic-pulmonary direction. Shumacker[31] advised against surgical treatment in one case of this type, and Dammann and co-workers[7] have expressed the belief that the condition is primarily nonsurgical. De Camp[32] reported one case in which death followed surgical treatment. In children, the problem is somewhat different in that one would not expect accumulated organic changes approaching irreversibility to be present. Here the question of an associated defect may be the main deterrent to surgical exploration. Exploration may be justified if studies of the type described give no indication of an associated intracardiac defect of severe nature. If the cyanosis has been present since early life, the likelihood of an associated defect is very great indeed.

Summary

In seven cases of patent ductus arteriosus with pulmonary hypertension a transient or maintained blood flow from the pulmonary artery to the aorta has been demonstrated. These patients were studied by cardiac catheterization and simultaneous blood sampling from radial and femoral arteries. Under given conditions in each case, the oxygen content of femoral arterial blood was demonstrated to be less than that of simultaneously withdrawn radial arterial blood.

It was possible to affect the magnitude and occasionally the direction of the aortic-to-pulmonary flow in each of these cases by varying the oxygen content of the gas mixture breathed.

This finding affords unequivocal evidence that in man systemic and pulmonary vascular pressures are affected differently by variations in oxygen content of the respired gas mixture. This effect affords a basis for tests which may be useful occasionally in the diagnosis of atypical ductus arteriosus since the pulmonary artery-to-aorta pressure gradient, and hence the flow in that direction, may be varied at will in the inverse direction to changes in oxygen tension of inspired air.

The injection of dye either into a peripheral vein or into the heart via the catheter and the recording of the dye-dilution curve from various sites in the arterial system, particularly the right radial and femoral arteries, has been of additional value, particularly in the quantitation of the magnitude of pulmonary artery-to-aorta flow. Dye entering the aorta via the ductus is demonstrable in the femoral artery, and on occasion may be detected in progressively diminishing concentration in arteries arising more proximally from the aortic arch. This last finding demonstrates that a significant degree of retrograde movement of blood may occur in the arch of the aorta in man.

Addendum

Since this manuscript was prepared, an additional patient, 21 years of age, has been studied in the laboratory while breathing varied oxygen mixtures, and the findings were practically identical with those of case 4. This young woman also showed the evidence of retrograde flow of blood in the aortic arch and the characteristic differences in dye curves obtained from various sites of the arterial tree.

Acknowledgments

Acknowledgment is made to Dr. Edward Morgan and Dr. Earl Beard, Fellows of the Mayo Foundation, who have made individual case presentations at local medical meetings. The help of Dr. J. E. Edwards of the Section of Pathologic Anatomy, Mayo Clinic, with particular regard to the postmortem and biopsy material is also acknowledged with sincere appreciation. The cooperation of Drs. O. T. Clagett and J. W. Kirklin, Division of Surgery, in the study is appreciated.

Sumario Español

Siete casos de conducto arterioso patente con hipertensión pulmonar y reversión de la dirección usual de la circulación se describen. Respiración de una mezcla baja en oxígeno o inició u aumentó el "shunt" reversado, y respiración de oxígeno al 100% produjo un efecto inverso. Diferencias en saturación de oxígeno y en curvas de dilución de tinte registradas simultaneamente de las arterias radiales y femorales hicieron posible calculaciones de la diferencia en proporción de sangre desviada circulando en estas arterias y demuestra que movimiento retrogrado de sangre en la aorta puede ocurrir.

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Mechanical and Myocardial Factors in Chronic Constrictive Pericarditis

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The hemodynamic findings in five patients are presented in order to demonstrate the variability in the clinical and physiologic patterns that may be encountered in restrictive disease of the pericardium. The mechanical effects of pericardial encasement previously described were confirmed. Furthermore, it was found that myocardial insufficiency and hypervolemia were not only important causative agents in the circulatory dysfunction but were in some measure reversible, thus permitting resolution of the congestive state and disappearance of the "typical" hemodynamic findings of constrictive pericarditis.

THE HEMODYNAMIC abnormalities of constrictive pericarditis were first described in 1946 by Bloomfield and associates[1] who stressed "the virtually normal (right) ventricular systolic pressure, a low ventricular pulse pressure, a marked elevation of the mean (right) auricular and ventricular diastolic, prominence of the early diastolic dip in the auricle and ventricle and a marked fall in auricular pressure during ventricular ejection, which, with the diastolic dip, give to the (auricular) tracing a distinct 'W' form." The presence of this diastolic dip was subsequently confirmed by Hansen and co-authors[2] who also described it in the left ventricular curve obtained during surgery and noted its disappearance after pericardectomy. In enlarging on the circulatory abnormalities of constrictive pericarditis, Burwell[3] confirmed the pressure pattern previously described[1] and showed further that there was a small pulse pressure in the pulmonary artery due to a large increase in diastolic and little or no rise in systolic pressure. He focused attention on left ventricular involvement by the pericardial encasement to account for this finding and consequently urged more complete stripping of the left heart surgically. In order to explain the hemodynamic findings more fully Burwell concluded that the stiffened pericardium imposed its own distensibility characteristic equally on the two sides of the heart. The detailed effects of experimentally produced constriction were explored by Isaacs, Carter and Haller[4] who noted, as was implied by Burwell,[3] that the volume-elasticity curves of the two ventricles become identical after experimental production of generalized constriction and that constriction of the ventricular chambers, rather than caval or auricular cavities, is the primary anatomic lesion.

In consequence of these publications, a more or less uniform picture has been accepted as characteristic of constrictive pericarditis, in which the mechanical effects of an inelastic pericardium have been stressed as of primary importance in the production of the clinical and hemodynamic findings.

As a result of studying a group of patients with pericardial disease, using the cardiac catheterization technic, it has become apparent to us that there may be considerable variability in the clinical and physiologic patterns encountered and that in addition to the mechanical factor, there may be an important element of myocardial insufficiency contributing to the circulatory disturbances. A series of five pa-

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tients will be presented to elucidate these points. The physiologic observations and their significance will be described and discussed separately in each of the five cases.

Methods

The methods of study, using the cardiac catheterization technic, have been described in detail elsewhere.[5, 6] All the cases were studied under basal conditions at rest, three of them after digitalization, and two of them during a steady state of exercise.

carditis.[1, 2, 3, 7, 8, 9] Preoperatively, the resting cardiac output and stroke volume were not greatly reduced from normal levels. There was pulmonary hypertension present which was almost entirely a diastolic hypertension, the pulse pressure remaining small. This accompanied a threefold increase in the right ventricular diastolic pressure and the usual early diastolic dip was present on the right ventricular pressure curve. The blood volume was considerably increased.

At operation a 5 mm. thick pericardium was found uniformly involving auricles, ventricles and the

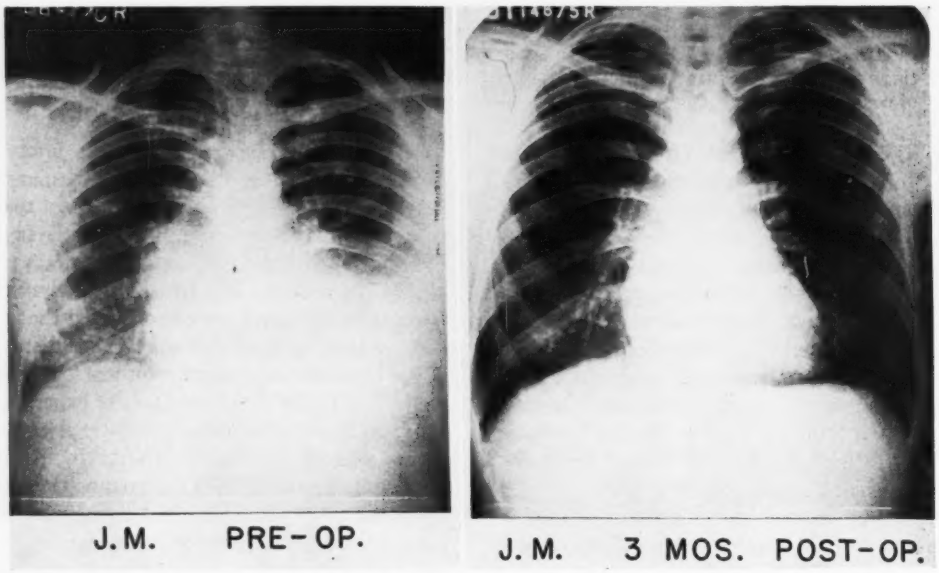

Fig. 1. Posteroanterior x-ray films of chest of patient No. 596, J. M., at the time of his first and second hemodynamic studies.

Results and Discussion

First, the importance of the mechanical factors and their effect upon hemodynamics will be analyzed in a patient studied preoperatively and after pericardectomy.

Case 1. This 36 year old Puerto Rican male (no. 596, J. M.) had a four year history of right upper quadrant pain, dyspnea, orthopnea and ankle edema, and on physical examination had a liver extending to the iliac crest and evidence of a left hydrothorax. Cardiac examination revealed a sinus rhythm, no murmurs, thrills or diminution in heart sounds. The etiology of his pericarditis was not known. The preoperative and postoperative x-ray films are seen in figure 1.

The hemodynamic data, (table 1, fig. 2) are similar to those reported as typical of constrictive peri-

venae cavae. An extensive decortication of all the chambers was carried out.

Three months later the liver edge lay at the costal margin, and the patient was free of symptoms. Measurements of cardiocirculatory function at this time were within normal limits and the ventricular diastolic dip was absent.

The hemodynamic alterations seen in this patient certainly appear to have been due to the presence of a poorly distensible pericardium. Obviously the thickened pericardium, which enclosed the entire heart, altered the distensibility of the auricles and ventricles and modified the conditions under which a normal venous return was accommodated. As a result of the alteration in distensibility of the right ventricle and auricle the diastolic pressure rose

in these chambers. Similarly diastolic pulmonary hypertension was the reflection of the reduced distensibility of the left heart. Whether the effects of the increased systemic venous pressure upon renal function eventually played a part in the development of hypervolemia can only be surmised.

A close inspection of the pressure abnormalities reveals several points of interest concerning this modification of distensibility. In this patient with pericarditis, preoperatively, the diastolic pressure in the right ventricle was 15 mm. Hg and the diastolic pressure in the pulmonary artery was 21 mm. Hg. Obviously the mean pressure in the left auricle and the end diastolic pressure in the left ventricle were at most 21 mm. Hg, and very likely less. Therefore, this rise was of the same magnitude as that of the end diastolic pressure in the right ventricle. It is known that the distensibility of the normal right and left auricles and ventricles is different, the right being more distensible than the left, which implies that the same increment of volume would tend to produce less pressure response in the right than in the left chamber. Hence it would seem that the most plausible explanation of an absolute rise of similar magnitude in diastolic, and hence venous pressure, in each side of the circulation is that the distensibility characteristic of the pericardium has been substituted for that of the individual chambers.[3, 4]

It is important to point out that an identical increment in venous pressure on both sides of the circulation has entirely different effects upon the dynamics of the systemic and pulmonary capillaries. Normally the systemic capillary hydrostatic pressure is close to the oncotic pressure, therefore small increases in systemic venous and hence capillary pressure result in a considerable increase in transudation of fluid from the systemic capillaries. Since the lung hydrostatic capillary pressure is normally around 5 mm. Hg, obviously much lower than systemic capillary pressure, there is a greater pressure differential or margin of safety, between oncotic and hydrostatic pressure in the pulmonary capillary system than in the systemic capillaries. Thus a rise in pulmonary venous pressure, even though it adds to the lung capillary hydrostatic pressure an increment of similar magnitude to the rise of systemic venous pressure, may not cause hydrostatic to exceed oncotic pressure and hence transudation into alveoli would not occur. This explains why with clinical evidence of considerable systemic congestion there is seldom, if ever, frank pulmonary edema in constrictive pericarditis.

Furthermore, it is noteworthy that the pulse pressure in the pulmonary artery is small, in contradistinction to the large pulse pressure seen in left ventricular failure. In the latter condition, heterodynamism of the two ventricles, the right being spared and capable of delivering more blood to the lungs than the left can eject into the systemic circulation, permits trapping of blood in the pulmonary bed with a rise in pulmonary artery blood volume and pulse pressure. The small pulse pressure in constrictive pericarditis indicates that heterodynamism of the ventricles probably does not exist.[3]

It is a matter of speculation whether the presence of a stiff pericardium actually influences the contractile mechanism of the encased myocardial fibers, in particular their tension and elongation. Although this might well be expected, it is quite interesting that in this case, as well as in some others with this same type of lesion, stroke volume is normal or only slightly reduced although the ventricular filling pressure is elevated considerably above normal.

Although it appears that during systole the ventricular musculature more or less successfully contracts against the forces of the inelastic pericardium, at the end of systole these forces become manifest suddenly, and the ventricle relaxes precipitously instead of in an isometric fashion. With this rapid change in the volume of the ventricular cavity there is a rapid fall in pressure which produces the postsystolic and early diastolic dip in the ventricular and auricular tracings. However, an alternative mechanism could be offered to explain this dip, namely, that the stiffened pericardium may, at the time of isometric relaxation, set into play a low frequency vibration producing an overshooting of the pressure curve. In any event, the dip appears to be a consistent finding

TABLE 1.—*Physiologic Measurements in Five Patients with Pericardial Disease*

Case	BSA	Cardiac Index (*L./min./M² BSA*)	Stroke Volume (*cc.*)	Heart Rate (*beats/min.*)	Oxygen Consumption (*cc./min./M² BSA*)	R.Q.	AV diff (*vol. %*)	Arterial Blood Oxygen		Pressure in mm. Hg			TBV (*cc./M² BSA*)	PV (*cc./M² BSA*)	H'crt (%)
								cont. (*vol. %*)	sat. (%)	Systemic Artery (*s/d, m*)	Pulmonary Artery (*s/d, m*)	Right Ventricle (*d*)			
#596 J. M.	(a) 1.87	2.60	56	86	119	0.82	4.6	16.6	93	118/77, 96	30/21, 23	15	4587	2512	45
	(b) 1.85	3.27	78	78	125	0.72	3.8	20.8	96	110/72, 90	18/8, 11	5	3650	1768	52
#638 J. R.	(c) 1.97	3.20	79	80	134	0.76	4.2	15.8	95	100/65, 81	35/17, 25	10	3340	1900	43
	(c′)	2.76	68	80	133	0.77	4.8	16.0	95	108/67, 80	37/17, 25	10			
	(d) 1.95	2.84	78	71	125	0.83	4.4	17.0	94	104/62, 78	31/17, 24	11	2987	1773	42
	(d′)	3.12	78	78	202	0.90	6.5	17.0	96	121/68, 88	43/22, 30	15			
#661 G. M.	(e) 1.76	2.84	63	79	131	0.78	4.6	20.2	95	115/70, 86	15/5, 11	2	2716	1338	51
#619 G. R.	(f) 1.75	1.62	38	75	131	0.92	8.1	19.8	97	121/84, 96	35/23, 28	21	5360	2480	53
	(f′)	1.97	58	60	139	0.94	7.0	19.5	98	126/76, 95	31/18, 22	16			
#647 A. G.	(g) 1.72	3.41	64	92	137	0.78	4.0	13.8	91	124/78, 98	33/19, 24	18	3765	2317	39
	(h) 1.63	2.88	49	96	138	0.80	4.8	17.3	91	97/66, 80	22/8, 14	5	3010	1685	43
	(i) 1.63	2.23	45	81	118	0.81	5.3	18.9	97	93/60, 70	18/8, 12	6	2598	1466	45
	(i′)	2.50	50	84	176	0.81	6.9	18.5	95	107/64, 82	18/9, 14	8			

(a) At rest, preoperatively; (b) at rest, 3 months postpericardiectomy; (c) control at rest, 1951; (c′) 46 minutes after intravenous injection of 1.25 mg. Digoxin, 1951; (d) control at rest, 1953; (d′) after 8 minutes of exercise, 1953; (e) at rest; (f) control at rest; (f′) 64 minutes after intravenous injection of 1.0 mg. Digoxin; (g) at rest, 1951; (h) at rest, 4 weeks later, 1951; (i) control at rest 24 months later, 1953; (i′) after 10 minutes of exercise, 1953.

ABBREVIATIONS: BSA = body surface area; AV diff = arteriovenous oxygen difference; TBV = total blood volume; PV = plasma volume; H'crt = hematocrit.

in chronic constrictive pericarditis, and, in the successfully operated case, disappears after pericardectomy, as it did in this patient.

The second case demonstrates the surprising fact that the classical hemodynamic abnormalities associated with constrictive pericarditis may exist in the absence of any clinical expression of circulatory congestion.

Case 2. This 47 year old white male (No. 638, J. R.) gave a story of pulmonary and laryngeal tuberculosis associated with mild dyspnea dating back 15 years. In addition there was a well documented story of tuberculous pericarditis with effusion in 1946 for which he received streptomycin. The x-ray film of this date is seen in figure 3. Subsequent films (fig. 3) have shown a reduction in heart size which has been stationary from 1948 to 1953. In 1951 he was admitted to Bellevue Hospital because of a small hemoptysis, but without other complaints.

Examination at this time revealed a sinus mechanism, no murmurs or diminution of heart sounds, and no evidence of an enlarged liver or edema. The first hemodynamic study in 1951 showed a normal cardiac output and a slight increase in blood volume (table 1, fig. 4). Mild pulmonary hypertension, a considerable elevation of the right ventricular diastolic pressure and the characteristic early right ventricular diastolic dip were all present. In the course of this study, the patient was given intravenous Digoxin and the only change observed was a fall in cardiac output of 14 per cent. This type of response to intravenous Digoxin has been noted in subjects in whom there was no evidence of congestive heart failure.[10] The patient was discharged and continued his usual activities as an itinerant salesman. Clinically he remained free of pulmonary or peripheral congestion and received no further medications.

In 1953, two years after his first study, he was re-evaluated. The only significant changes in the hemodynamic findings (table 1, fig. 4) were a slight fall in cardiac output which still lay within normal limits and a slight reduction in blood volume. On mild exercise, which in a normal subject would cause a rise in blood flow of at least 600 cc. for every 100 cc. increase in oxygen consumption,[11] there was only an increase of 330 cc. With this small increase in cardiac output, pulmonary artery and right ventricular hypertension became aggravated. Since myocardial failure in the usual sense appears to have been eliminated as a factor by the Digoxin study, it would appear that the abnormal findings on exercise were caused by the restrictive effects of the pericardium upon filling and contraction of the heart.

Hence at rest and during exercise there is evidence that the diseased pericardium adversely affected the circulation despite which the clinical manifestations of this lesion were absent. Why then did not this patient show the classic clinical signs, namely edema, a large liver and ascites? Was the degree of cardiac restriction due to stiffening of the pericardium not great enough to limit cardiac output nor to elevate venous pressure to a critical level above which edema is observed, or is it that myocardial function, although altered by this

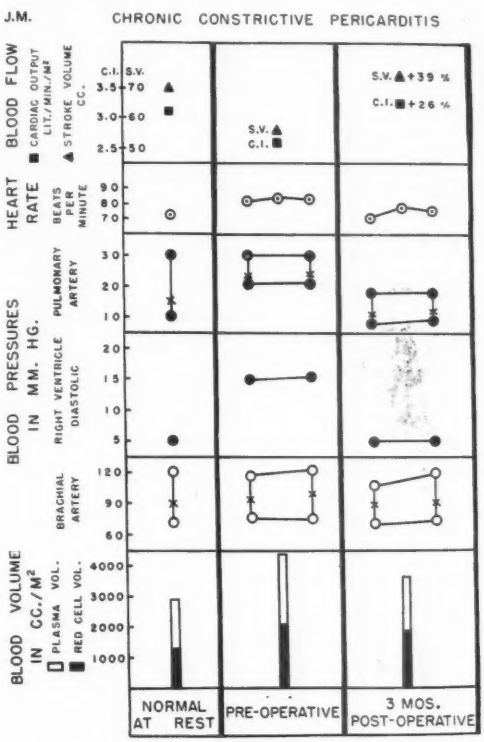

FIG. 2. Graphic representation of the hemodynamic findings, pre- and postoperatively in patient No. 596, J. M. Note a rise of 39 per cent in stroke volume and of 26 per cent in cardiac index postoperatively. For further discussion see text. In this and all subsequent figures closed triangles = stroke volume; closed squares = cardiac index; target dots = heart rate; closed circles = pulmonary artery systolic and diastolic, and right ventricular end diastolic pressures; open circles = brachial artery systolic and diastolic pressures; cross marks = mean pressure; the black bar graph = red cell volume; the white bar graph = plasma volume. The normal values are plotted in the first vertical column.

abnormal pericardium, is still able to perform well under this duress? It is possible that this patient with evidence of hematogenous tuberculosis may have had some adrenal insufficiency and alteration in salt and water metabolism sufficient to prevent edema formation. Be that as it may, at the time of the first study it was decided not to subject the patient to pericardectomy in the absence of the clinical criteria. After a two-year follow-up during which he led a fairly active life it would seem that the lack of change in the clinical as well as the physiologic status still justifies surgical abstention.

That stiffening of the pericardium is not always productive of hemodynamic or clinical abnormalities is clearly shown in the next patient, where the presence of a calcified pericardium was not attended by any alteration in the dynamics of the circulation.

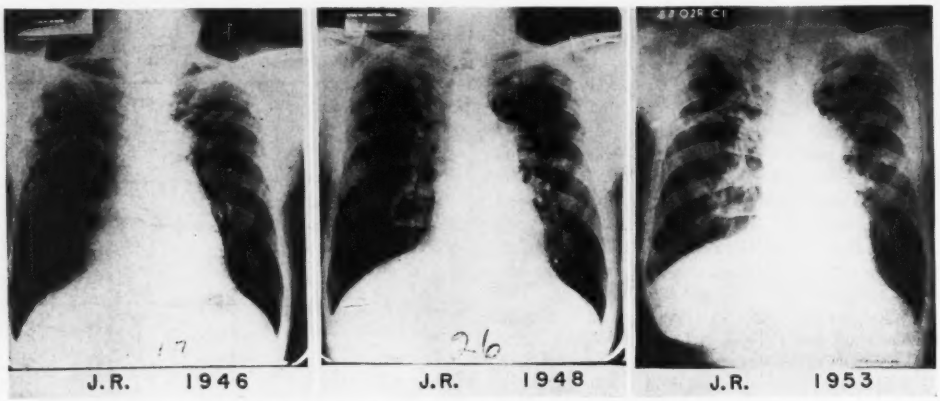

FIG. 3. Posteroanterior x-ray films of patient No. 638, J. R. For discussion see text.

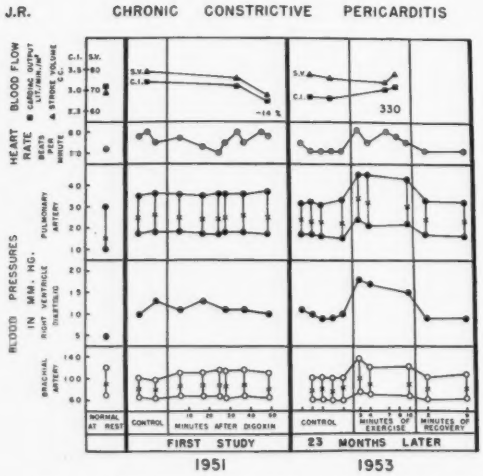

FIG. 4. Graphic representation of the hemodynamic findings in patient No. 638, J. R. The patient received 1.25 mg. Digoxin intravenously at the time of the first study and 23 months later, at the time of the second study, the response to exercise was determined. The value 330 which appears in the exercise column refers to the blood flow increase in cubic centimeters per 100 cc. oxygen consumption increase. For discussion see text.

Case 3. (No. 661, G. M.) This 59 year old white male had an extensively calcified pericardium of unknown cause (fig. 5); nevertheless, there were no objective findings of either pulmonary or peripheral congestion. The tracing from the right ventricle of this patient (fig. 6) did not show the early diastolic dip. Furthermore there were normal pressures in both the greater and lesser circuits and a normal blood flow and blood volume (table 1). Certainly this calcified pericardium was not interfering with the patient's circulation at rest.

The observation that a calcified pericardium need not embarrass the circulation has been known clinically for some time and suggests that it is the degree of cardiac restriction which may follow pericardial disease rather than stiffening alone, that plays an essential role in the development of the clinical or hemodynamic picture.

In sharp contrast to the cases previously described, the physiologic studies made in the

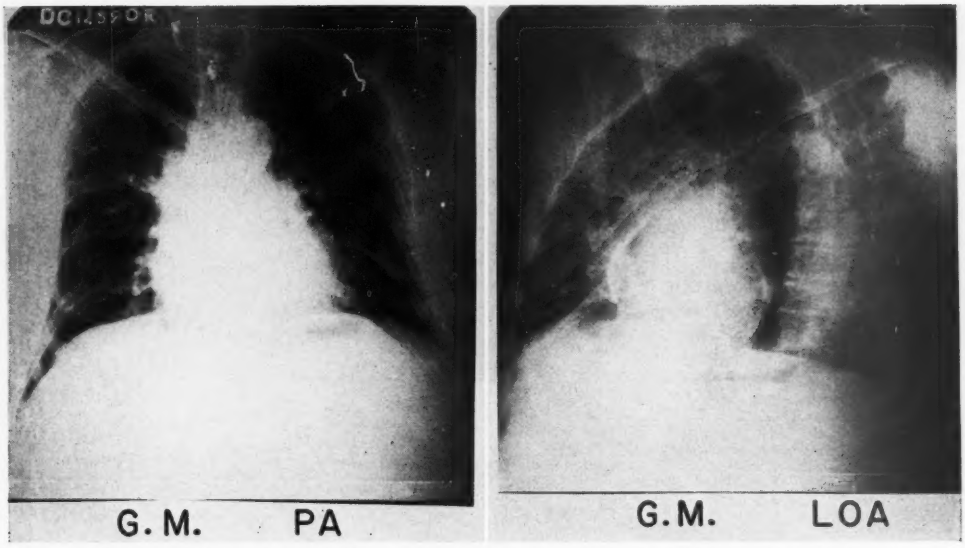

FIG. 5. Posteroanterior and left anterior oblique x-ray films of patient No. 661, G. M.

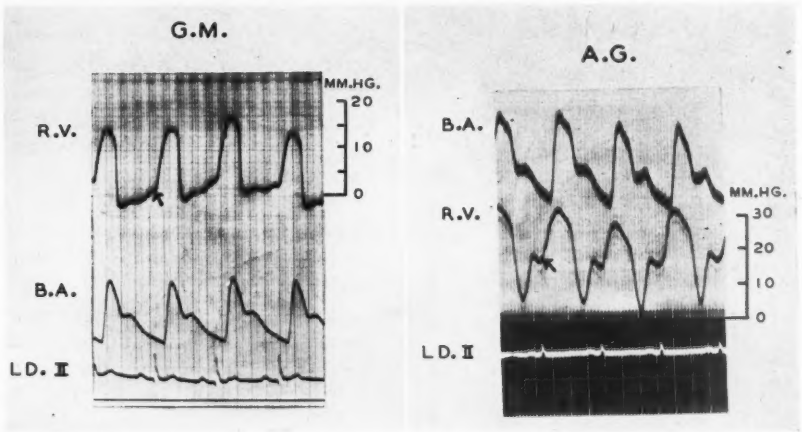

FIG. 6. Pressure tracings from the right ventricle (R.V.) and brachial artery (B.A.) and electrocardiographic lead II (LD. II) of patient No. 661, G. M. on the left and of patient No. 647, A. G. on the right. The vertical time lines are 0.04 second apart. The tracings on the left were recorded by Statham gage pressure transducers and the cathode ray oscillographic technic for registering blood pressures on photographic paper. The curves on the right were recorded by Hamilton manometers. The arrow indicates the end diastolic point of the right ventricle.

next patient emphasize the fact that failure of the myocardium may contribute in considerable measure to the congestive state in constrictive pericarditis.

Case 4. This 28 year old white male (No. 619, G. R.) had only a two-month history of edema and dyspnea. At the time of examination he was found to have auricular flutter with a high degree of A-V block and a slow ventricular rate. No murmurs were heard, nor were the heart sounds faint. A diastolic gallop was audible at the apex. Calcium was present in the pericardium as seen in the x-ray films (fig. 7). The liver edge was palpated four finger breadths below the costal margin. No definite etiology of the pericarditis was established.

In contrast to the first case the cardiac output was considerably reduced. However, many

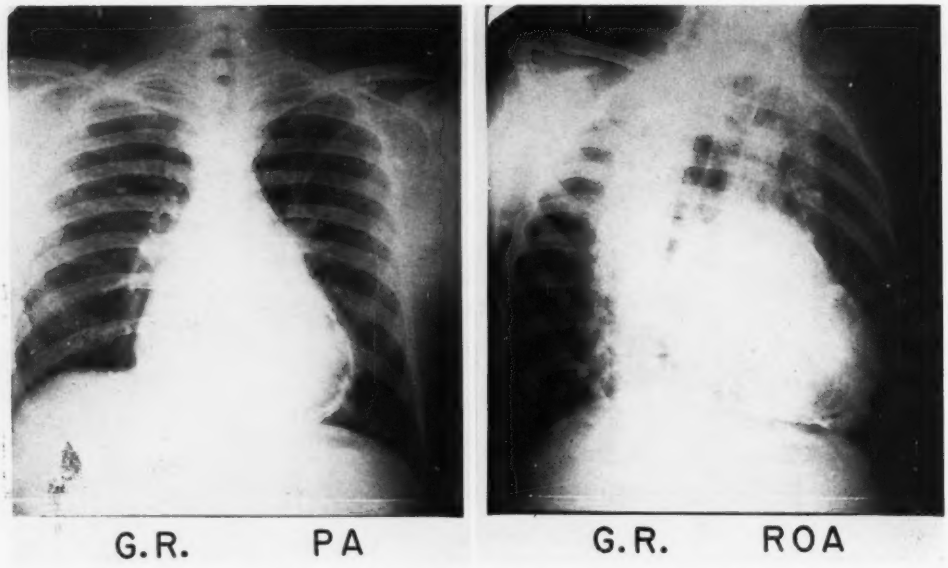

FIG. 7. Posteroanterior and right anterior oblique x-ray films of patient No. 619, G. R.

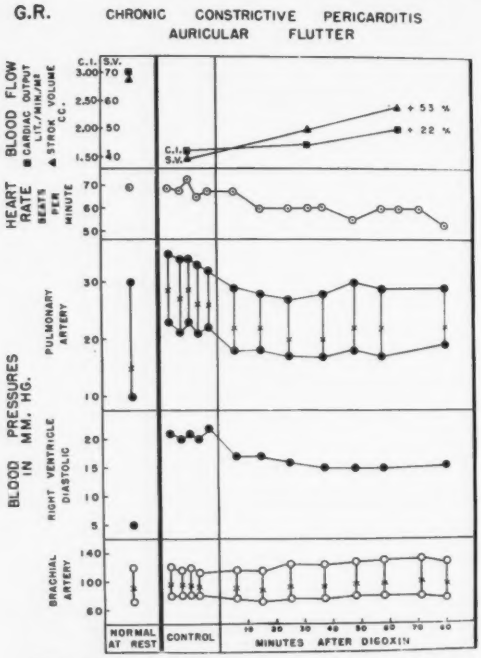

FIG. 8. Response to intravenous Digoxin (1.0 mg.) in patient No. 619, G. R. Note that the postdigoxin cardiac indices rose 7 per cent and 22 per cent respectively and the corresponding stroke volume 32 per cent and 53 per cent. For further discussion see text.

of the other hemodynamic features were characteristic of constrictive pericarditis since the pulmonary artery pulse pressure was small with a high diastolic and only a slight elevation of systolic pressure. The right ventricular diastolic pressure was elevated (table 1), and the early diastolic dip was apparent. It should be noted that there was a considerable degree of hypervolemia. Immediately following the administration of intravenous Digoxin the cardiac output rose, and even before there was a slowing of the ventricular rate, there was a significant fall in the pulmonary artery and right ventricular pressures (fig. 8). This response is characteristic of a failing myocardium in which improved ventricular emptying follows the administration of the glycoside[5, 6] and, therefore, this acute Digoxin study demonstrates the existence of myocardial failure in this individual with constrictive pericarditis. The fact that the pulmonary artery and right ventricular diastolic pressures were still elevated at the conclusion of the study (80 minutes after the administration of Digoxin) might be ascribed to the persistent mechanical interference of the pericardium. However this explanation cannot be offered without reservation because experience with other patients in congestive failure and

marked hypervolemia, but without pericardial disease, has shown that the complex readjustments set into play by the glycoside may not restore the intracardiac pressures to a normal state for a considerable period of time.[6, 12]

In summary this case serves to emphasize the important role that myocardial failure may play in this disease. Since further definitive studies are not available either after prolonged medical regime or after pericardectomy, the role played by the stiffened pericardium in this man was not further elucidated.

In the last patient of this group, serial measurements over a two-year period revealed that all the clinical and physiologic findings which were present at the time of the initial study and which could have been ascribed solely to the mechanical effects of constrictive pericarditis proved to be reversible on a medical regime alone. This unexpected modification of the first hemodynamic pattern again raises a question as to the exact nature and detailed mechanism of this disease.

Case 5. This 43 year old white male (No. 647, A. G.) had a nine-year history of pericardial involvement. In 1944 he was hospitalized because of complaints of severe dyspnea and anasarca. Examination revealed evidence of pericardial effusion, hydrothorax, enlarged liver and generalized edema. After a four-month regimen which included pericardial taps totalling 1000 cc. of fluid, thoracentesis, mercurial diuretics and digitalis he was discharged considerably improved. An intensive search at this time for the cause of his pericarditis was unrewarding but later on (in 1952) he developed a minimal lesion of pulmonary tuberculosis. He returned to work as a laborer, and discontinued all medications. For two years he remained asymptomatic. In 1946 he returned with the same complaints and findings although he was not as ill as previously nor was there thought to be a significant amount of pericardial fluid. Again a medical regimen abolished evidence of congestion. X-ray films at the time of his first and second admissions are in the first two frames in figure 9, and in the last frame is a follow-up film taken in 1947. He remained well, at work, and without medication until 1951 when he reappeared dyspneic and edematous. Examination of the heart showed no murmurs or dimunition in heart sounds. For the first time x-ray films revealed evidence of pericardial calcification as indicated by the arrow in figure 10.

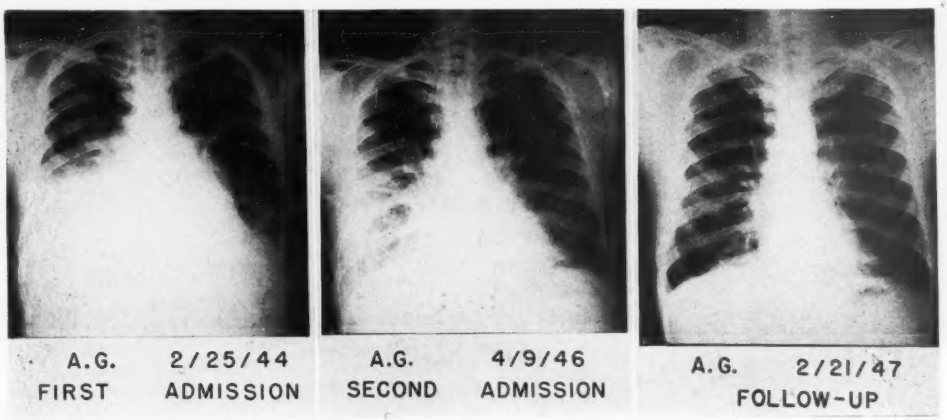

FIG. 9. Posteroanterior x-ray films of patient No. 647, A. G. For discussion see text.

It was at this time that he was first studied (table 1 and fig. 11). The cardiac output was at the upper limits of normal. All the other hemodynamic findings noted in the first case were present, namely a high diastolic and small pulse pressure in the pulmonary artery, a high diastolic pressure in the right ventricle and the characteristic dip in the ventricular curve (fig. 6). The blood volume was also markedly elevated.

Following this study he was kept on bedrest, digitalized, and given diuretics. Four weeks later, following marked clinical improvement and alleviation of all signs and symptoms of congestion, he was restudied. At this time the cardiac output was lower, the pulmonary artery pressures were normal, and the right ventricular diastolic pressure almost normal. There had been also a large reduction in blood volume. The right ventricular and auricular curves, however, still showed the dip. There was a

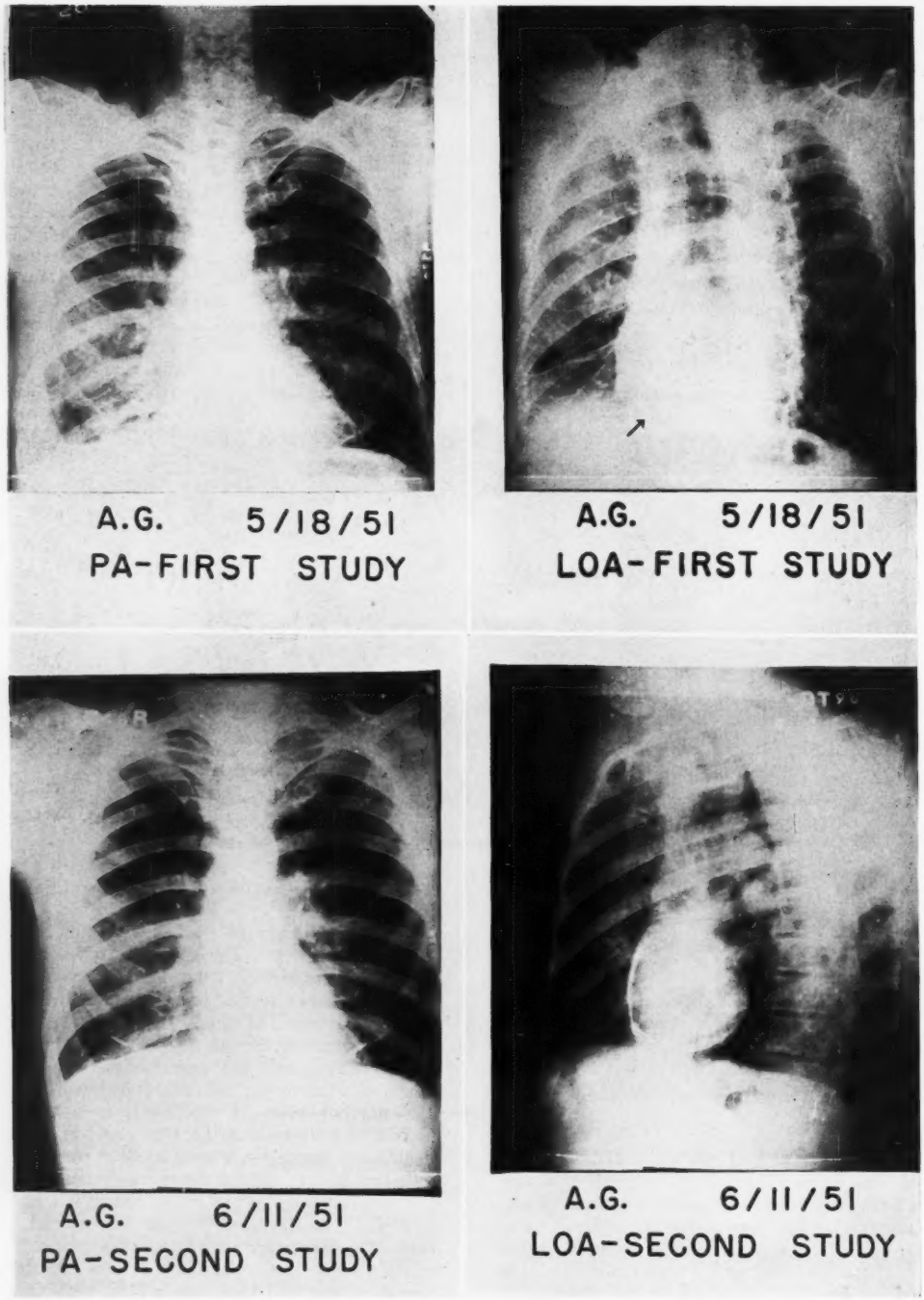

FIG. 10. Posteroanterior and left anterior oblique x-ray films of patient No. 647, A. G. The upper two x-ray films were taken at the time of the first study and the lower two at the time of the second. For discussion see text.

striking diminution in heart size as can be seen in figure 10. The patient was discharged and remained on digitalis. Six months later he developed a minimal lesion of pulmonary tuberculosis for which he received six months of bedrest and streptomycin. Another period free of symptoms, this time without medication, ensued. However, in December 1952 dyspnea and weight gain prompted redigitalization and resulted in relief of dyspnea. Five months later he suffered from severe paroxysmal nocturnal dyspnea, had a protodiastolic gallop and pulmonary rhonchi. He was therefore hospitalized and mercurial diuretics were added to the digitalis therapy. After one month he was restudied and at this time no gallop, rhonchi or other signs of congestion were present. The heart size and degree of calcification were unchanged and the x-ray films resembled those made June 11, 1951.

This third hemodynamic evaluation demonstrated pulmonary artery and right ventricular pressures which were the same as on the second study, that is, within normal limits save for a slight elevation in the diastolic pressure of the right ventricle. The blood volume was the lowest recorded on this patient. However, cardiac output was now definitely lower than normal at rest and its increase during leg exercise was limited to 466 cc. per 100 cc. of increase in oxygen consumption. During this exercise, with a level of cardiac output which was less than that of a normal subject at rest, the pressure in the pulmonary artery remained within normal limits although the diastolic pressure in the right ventricle was definitely abnormal. The exercise response of this patient (table 1 and fig. 11) should be contrasted with that of the second case (no. 638) in whom restriction was felt to be responsible for the pulmonary hypertension at rest and its aggravation on exercise. The dip still persisted in the ventricular and auricular tracings.

In the light of these follow-up studies one cannot escape the conclusion that there was a reversible phenomenon which was largely responsible for the original congestive state of this patient, particularly since his improvement has been more or less maintained on a medical regimen for a period of two years. Since both the clinical and hemodynamic phenomena were reversible, it is difficult to accept the mechanical interference of pericardial constriction as the sole agent in the production of this picture. Actually the degree of restriction was probably less than in other cases, and a reduction in the capacity of the pericardial sac was only a hindrance to the circulation when other factors, namely myocardial insufficiency and hypervolemia were present.

The following observations may be cited to support the interpretation that a relatively small degree of pericardial restriction existed. First, one notes the absence of pulmonary hypertension even on exertion once congestion had been relieved, in sharp contrast to the second case (No. 638), whose restriction was severe enough to produce pulmonary hypertension at rest and aggravate it on exercise, even though he also was not in a congestive state. Second, diminution in the size of the cardiac silhouette between the first two studies indicates that the volume of the heart was not determined solely by the fixed pericardium and that the peri-

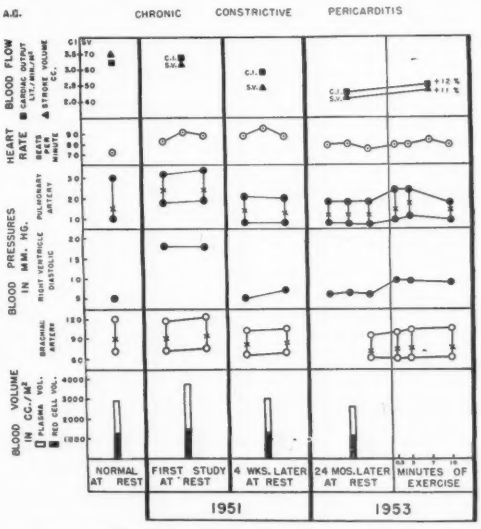

FIG. 11. Graphic representation of the hemodynamic findings in patient No. 647, A. G. before and after relief of congestive failure. For discussion see text.

cardial wall was able to yield when the length of the myocardial fibers was reduced. In spite of the small degree of pericardial restriction one cannot escape the conclusion that when the patient was in the congestive state this degree of restriction did influence the hemodynamic picture since the pressure pattern encountered at the time of the first study was indistinguishable from that observed in the first case (No. 596) before pericardectomy.

Analysis of other varying hemodynamic features points out the important part played by the state of the myocardium and by hypervolemia in the progress of this man's disease.

It should be noted that the cardiac output was highest in the congestive state and that as the cardiac output decreased the blood volume also fell. It is tempting therefore to relate these two functions and raise the question as to whether the hypervolemia of itself influenced the level of blood flow, since it has been found in some other forms of congestive heart failure that hypervolemia is a primary factor in increasing blood flow and in bringing about failure of the myocardium.[13] At the time of the third study the level of cardiac output was so markedly reduced at rest and rose so little on exercise that one must assume that the integrity of the myocardium itself was compromised.

It is impossible to reconstruct with any degree of certainty the sequence of events which transpired throughout this patient's illness. One could however postulate, for example, that a mild degree of restriction remained in this man after the initial phase of pericardial inflammation subsided. This restriction was adversely influential only during bouts of severe exertion associated with the patient's resumption of his normal activity as a manual laborer, when it produced a rise in ventricular diastolic pressure together with an inadequate response in blood flow. These in turn stimulated progressive hypervolemia and thereby an increasing venous return to the point where the diastolic residual volume of the heart was large enough and dilatation of myocardial fibers great enough to be influenced by and assume the distensibility characteristics of the restricted pericardium at rest. At this stage all the findings resembled the so-called typical restrictive phase of the disease. It may well be that myocardial insufficiency, apart from the mechanical factors, supervened at some point and further contributed to the congestive state. The nature of this myocardial insufficiency is unknown but may be related to the original inflammatory process, perhaps by contiguity, or may result from the stress imposed by the stiffened pericardium on the cardiac muscle.

In summary, one can only say that increased cardiac residual volume associated with generalized hypervolemia, some restriction of the pericardium and the effects of abnormal myocardial function are probably all involved in producing the physiologic patterns described. Perhaps no one factor alone was abnormal enough to destroy circulatory compensation, but the interplay of all three combined to generate the congestive state.

Summary and Conclusions

1. Five patients studied by means of the cardiac catheterization technic are presented in order to analyze the factors contributing to circulatory dysfunction in restrictive disease of the pericardium.

2. It is noteworthy that the clinical as well as the hemodynamic picture was not the same in any of the five subjects. In one, the mechanical factor proved to be the dominant agent. In a second, the classic hemodynamic abnormalities of chronic constrictive pericarditis were found to exist in the absence of any clinical expression of circulatory congestion. A third patient demonstrated that a calcified pericardium need not be attended by any circulatory disturbance. Myocardial failure was shown to contribute to the congestive state in a fourth patient. The reversibility of the typical clinical hemodynamic pattern of congestion on medical management alone in a fifth subject posed the question as to what was the primary cause of his abnormalities.

3. Previous hemodynamic analyses have presented a more or less uniform picture of constrictive pericarditis laying the basic disturbance to the mechanical effects of the encasement. In this report analysis of the hemodynamic pattern which in four of the five patients with pericarditis initially was quite similar to that previously described, has revealed however that all the disturbances could not be ascribed solely to mechanical restriction of the heart. Indeed it was found that myocardial insufficiency and hypervolemia were not only important causative agents in the circulatory dysfunction but by proving to be in some measure reversible, permitted resolution of the congestive state and disappearance of the "typical" hemodynamic findings of constrictive pericarditis.

4. It is obvious from these findings that considerable study should be given to the developmental changes which occur as this disease

progresses and to the relative importance and interplay of such factors as the variation in the restrictive action of the pericardium, myocardial function and hypervolemia.

Acknowledgment

The authors gratefully acknowledge the cooperation of Dr. E. H. Luckey and the staff of the Second (Cornell) Medical Division, Bellevue Hospital, and of Dr. Jere Lord and the staff of the Fourth (New York University) Surgical Division, Bellevue Hospital, in making some of these patients available for study.

Sumario Español

Se presentan los hallazgos hemodinámicos en 5 pacientes para poder demostrar la variabilidad en los patrones clínicos y fisiológicos que puedan encontrarse en enfermedad constrictiva del pericardio. Los efectos mecánicos de constricción por el pericardio previamente descritos se confirman. Además, se encontró que insuficiencia del miocardio e hipervolemia no solamente fueron causas importantes en la disfunción circulatoria pero también probaron ser en alguna medida reversibles, así permitiendo una resolución del estado congestivo y desaparición de los hallazgos hemodinámicos típicos de la pericarditis constrictiva.

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Further Considerations on the Indications for and Limitations of Direct Surgery in Arteriosclerosis

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Segmental obstruction due to arteriosclerosis may occur in peripheral arteries. Further experience in resection of these obstructed segments and their replacement by vein grafts is reported. Replacement of segments of the femoral artery has been accomplished in 30 patients. The proper selection of patients is essential for success. The various causes of failure and the limitations of the procedure are emphasized.

THE APPLICATION of the principles of thromboendarterectomy and vein or arterial graft replacement for segmental obstruction in arteriosclerosis is not new. In earlier communications[1, 2, 3] we have briefly summarized the history of the efforts in this field. In these papers we have reported additional experience of our own, attempting to define indications for such procedures, limitations of their application and recording details of technic.

The purpose of this paper is to report our subsequent experience in the field, to re-emphasize certain principles laid down earlier and, particularly, to analyze the failures in an effort to discover the causes for unfavorable results.

We have, at the writing of this paper, replaced an obstructed segment of the femoral artery in 30 patients (bilaterally in 1). Of these 31 grafts, 16 were successful* and 15 failed. Both grafts were successful in the one patient who had both femoral arteries operated upon. Among the successful cases there were 4 saphenous homografts, 2 femoral autografts and 10 saphenous autografts (2 in one patient). The oldest of the autografts is 23 months, of the homografts 17 months. There have been 15 patients in whom femoral grafts have failed. Of these three have been homografts. One of them was not completed because of technical difficulties, but is grouped with the failures. The other two remained patent and functional postoperatively but closed at two and four months respectively. The remaining 13 failed immediately or shortly following implantation and were never functional. Except the two homografts mentioned above, none of the grafts has closed once its patency was definitely established postoperatively.

This paper does not include our experience with replacement of aortic bifurcation[3] or thromboendarterectomy.[1, 2, 3] The latter has been abandoned as a definitive procedure in favor of vein auto- or homograft in the femoral system and has been retained only for use in the iliac arteries.

SELECTION OF PATIENTS

Among the large number of individuals suffering from arteriosclerosis, candidates for segmental resection represent a relatively small group. The incidence of such cases is difficult to estimate. Robb,[4] from "the study of a large number of arteriograms and anatomical dissections . . . over a period of years," concludes that "fully 66 per cent of all patients with intermittent claudication or gangrene of the toes have a lesion in their arteries which is anatomi-

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* "Successful graft" as used throughout this paper refers to a graft which remains patent after placement and also supplies relief of symptoms such as intermittent claudication.

cally suitable for an artery graft. In actual fact, less than 20 per cent of these patients are suitable, the majority being rendered unsuitable by the manifestations of arterial disease such as involvement of the coronary or cerebral arteries, etc." He would undoubtedly include in this group patients in whom the pathology is so severe and so generally distributed that even though localized obstruction in main arterial channels is present the vessels distal to such areas are too narrow to carry sufficient blood for normal function of the extremity.

Candidates for therapy of this type are patients who suffer primarily from claudication. It is this symptom which prompts them to seek medical attention and, as will be seen later, if other symptoms are present the likelihood of success is markedly diminished. In an effort to determine the limits of this form of surgical therapy we have operated upon a number of patients who were definitely in a borderline category. Our series is still small and certainly no statistically significant conclusions can be drawn from it. Even at this point, however, certain definite indications and particularly contraindications would appear to stand out. There is one basic finding common to all candidates for superficial femoral artery resection; namely, the presence of a femoral pulse and the absence of one at the popliteal level. This does not necessarily mean that the obstruction is limited to the superficial femoral artery, but it is the broad base for the beginning of the selection of possible candidates for this type of surgery.

The age of the patient appears to be of little importance. Arteriosclerosis, particularly atherosclerosis, is not necessarily a disease of the aged. Those patients in which the grafts were successful ranged in age from 36 to 54 years, the average being 52. Among those in whom the grafts failed, the ages ranged from 33 to 66 years, the average age being 51.

Rest pain is considered to be a most important factor. Of the patients in whom the grafts were successful none had this symptom, while 7 of the 15 failures were in patients who complained of rest pain. The ischemic pain of arteriosclerosis in most instances denotes an involvement of a large number of arterioles, and rapid flow of blood through the vein graft, which is necessary for its continued patency, is not likely to occur. At this point in our study rest pain is considered a contraindication to femoral artery resection.

Trophic changes, such as ulceration or gangrene of a toe or other portion of the foot, are in the same category as rest pain. In none of the patients with successful femoral grafts were trophic changes present, while in four of the patients in whom the grafts failed there was an ulcer of one toe.

FIG. 1. Arteriogram showing good filling of the profunda femoris and a reasonably satisfactory lower segment of the superficial femoral artery. There is some disease of the latter but the patient, if clinically satisfactory, is a candidate for femoral artery resection and graft. The presence of rest pain, however, in the patient was a contraindication to the surgery. The graft in this patient failed.

Arteriography has been one of the most reliable aids in the selection of patients for femoral grafting. In some instances, however, the favorable appearance of the vessels in x-ray films has lead us to attempt surgery against our better judgment; that is, when rest pain and/or trophic changes were present in the feet (fig. 1). For the most part, the presence of a channel distal to the obstructed segment has been considered a prerequisite to surgery. Not

all of our early cases showed this distal segment, but we believe this to be due in some instances to errors in technics such as (1) the insertion of the needle into the profunda femoris artery, (2) the injection of insufficient contrast media, (3) slow injection and (4) exposure of the film before the media has reached the distal segment. At the present time we do not hesitate to repeat the arteriogram if the first one gives questionable information. In a number of cases, even though a distal segment was not visible

FIG. 2. Arteriogram showing heavy shadow of the profunda femoris as compared with that of the superficial femoral artery, partially blocked in this arteriogram. At surgery the latter vessel proximal and distal to the occluded segment, was found almost occluded by atheroma and having only a thin ribbon-like channel along one side.

and in an effort to define the extreme limits of surgery for segmental block, exploration of the popliteal artery was carried out. Clinically unfavorable cases failing to show a distal channel arteriographically in no instance had an open channel on surgical exploration. In those clinically favorable, that is, without atrophic changes or rest pain, the distal channel at the time of exploration was usually open.

The degree of disease as shown by the arteriogram would appear to be of importance in the selection of patients. In the main this is true although some successful cases showed a fair extent of filling defects of the lumen above and below the site of obstruction. Of particular importance is the presence of reasonably normal vessels below the bifurcation of the popliteal artery. Because of technical inadequacies these vessels are not always visible, but when a distinct pattern is obtained and the vessels are "moth-eaten" and disappear in the upper portion of the lower leg the prognosis is poor.

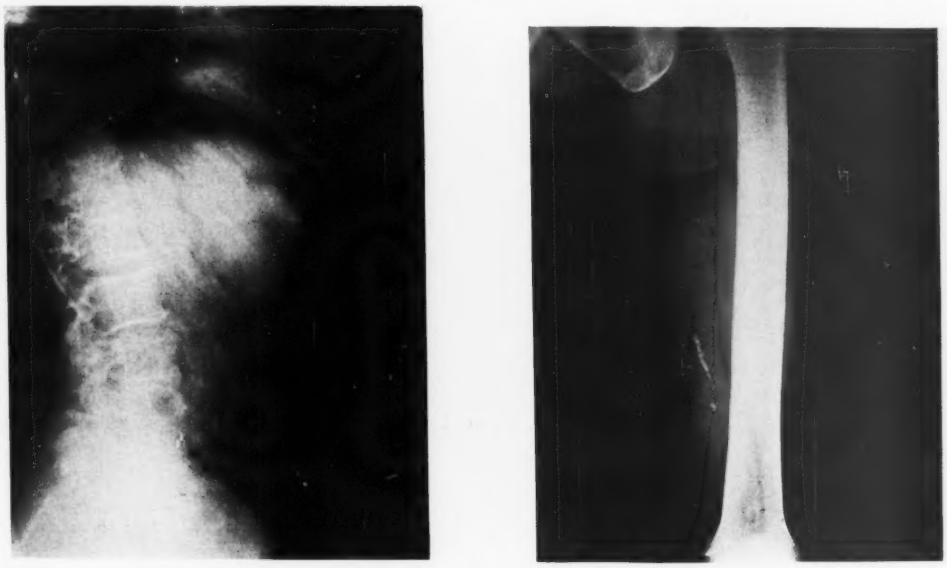
Occasionally the profunda femoris will show a heavy white pattern and if the proximal and distal superficial femoral segments are visible they may be of a uniformly pale quality (fig. 2). At surgery these segments may prove to be almost occluded by atheroma, each having only a thin ribbon-like channel along one side which, when seen en face in the x-ray, appears to be a good channel. We have referred to this phenomenon as "ribbon channels." The outlook in such instances is unfavorable.

Occasionally the profunda femoris will show signs of extensive disease. In our experience this vessel remains healthy in most instances longer than does the superficial branch, and any real degree of disease in the profunda is considered a contraindication to superficial femoral artery surgery.

It is interesting that calcification, per se, is not a uniformly satisfactory guide. One would hesitate to operate upon a patient with moderate to severe calcium deposits in the vessels in question, but a number of our successful cases showed such calcification. One patient with marked calcification of the abdominal aorta and somewhat less calcium in his pelvic and femoral vessels (fig. 3) had a successful iliac thromboendarterectomy on one side and a homologous vein graft in the opposite femoral artery. The one patient with bilaterally successful femoral grafts had a moderate amount of calcium in both superficial femoral arteries. By the same token, an absence of calcium is not necessarily a hopeful sign. Calcification was not particularly prominent in any of the failures, and in some there was none to be seen roentgenologically.

The factor of the number and size of collateral vessels has been included in this study.

The absence of trophic changes and rest pain and the presence of an open distal channel are obviously dependent upon an adequate collateral circulation. Whether the character of the appearance of the collateral vessels arteriographically can be used to any degree, however, in the selection of patients for surgery is questionable. One point of interest during the surgical procedure has been the backflow from the distal segment. The presence of backflow does not necessarily mean open tibial vessels. A good collateral artery entering just distal to the lower point of section of the femoral artery may well provide a substantial backflow. It is important not to injure a sizable collateral vessel coming into the distal segment (fig. 4), since in the event of failure of the graft the intact collateral vessels may mean the difference between the maintenance of the preoperative clinical state and a worsening of it. In one of our cases in which a large collateral vessel was sacrificed subsequent amputation was necessary. In some cases it has seemed desirable and even necessary to extend thromboendarterectomy past the lumen of such collateral vessels in order to complete a graft. We have done this successfully, recognizing at the time the possibilities of subsequent thrombosis, a risk present in all instances of thromboendarterectomy.



a *b*

FIG. 3. Roentgenograms showing marked calcification of the aorta (*a*) and similar though less extensive calcium deposits in the femoral artery (*b*). These findings would ordinarily deter the operator from surgery on such vessels. This patient, however, had an intimectomy of one common iliac artery and graft replacement of the femoral artery of the opposite side. Both vessels are open 9 and 16 months later.

TECHNICAL DETAILS OF SURGERY

The second group of factors bearing directly on the outcome of blood vessel replacement has to do with the technical details of surgery. Among these factors the type of graft stands out in importance. Certainly, where possible the patient's own tissue should be used, but unfortunately such a graft is not always available. In recent years the increased interest in vascular surgery has provided many types of substitutes for blood vessels, but because in this series of cases we have used only vein grafts, other types of substitutions will not be considered. The first two grafts were autogenous superficial femoral vein segments, measuring 10 and 8 cm. respectively. These were

successful and the patients are asymptomatic 23 and 22 months respectively. This type of graft is considered less desirable than the saphenous vein for two reasons: (1) A vein, regardless of the site, under arterial pressure will usually dilate to twice the size of the concomitant artery. This makes for turbulence of blood flow at the change of luminal diameters and as shown experimentally by Schmitz has appeared to promote clotting.[5] (2) Depending on

FIG. 4. Arteriogram showing the presence of a large collateral vessel just distal to the lower end of the obstructed segment. The injury or sacrifice of such a vessel may, in the event of failure of the graft, result in the loss of the patient's leg. This hazard may inhibit the surgeon in his effort to obtain a satisfactory distal segment for anastomosis.

the length of vein segment used and the collateral venous return, stasis may result from the excision of a vein segment. Though neither of these complications occurred in our cases the hazards must be recognized. The saphenous autograft on the other hand, dilates to approximately the size of the superficial femoral artery and at this site, where it is supported by muscle and fascia, becomes an ideal graft. Where, because of previous thrombosis or stripping, it is not available, a homologous saphenous vein may be used. In our series such a graft, taken by stripping just prior to implantation, has been used in six instances. Four of these are still open and functioning, the oldest, 25 cm. in length, now in situ for 17 months. A seventh included in this group as a failure was never implanted. Because of extreme friability of the host's vessels the graft had to be taken down after implantation and the proximal and distal host segments ligated. Two functioned originally and then closed at two and four months respectively following implantation. The second was removed six months postopera-

FIG. 5. Photomicrograph of a late occlusion (four months) of a saphenous homograft showing organizing thrombus in the lumen with thickened intima and fibrous media and adventitia.

tively and showed an organized clot within the lumen, a thickened intima with subintimal granulation and almost complete replacement by fibrous tissue of the media and adventitia. The signs of inflammation usually seen early in homografts were not present. It is assumed that the intima is that of the host. It is interesting to compare this with a saphenous autograft removed four months following implantation showing a well organized thrombus and intimal thickening. There was no inflammatory reaction. The remaining replacements, 22 in number, were saphenous autografts. Of these 13 failed and 9 were successful. The oldest of the latter grafts, 15 cm. in length, has functioned for 21 months. The longest successful

graft in this series is a 38 cm. saphenous autograft and has been in situ for 16 months. We have seen no correlation between the length of a graft and success or failure. The diameter of the graft in relation to the host vessel has been mentioned earlier. In general, the saphenous vein will dilate to the proper size for femoral artery replacement, though one of our failures was attributed to technical difficulties arising from a saphenous vein being too small.

The character and disposition of the blocked segment of femoral artery are of importance. In some of our cases it has been removed and the graft laid into its bed. In others it has been left in situ and both ends ligated. Because of the apparent complete obliteration of the lumen in one instance the ends were left free, that is, without ligature, and a hematoma developed following surgery. On exploration, it was found that the bleeding was coming from one of the open ends of the blocked segment. It is assumed that the increased flow of blood through the collateral vessels resulting from the graft was sufficient to force blood through the small remaining lumen of the blocked segment. Humphries[6] states that such a segment, left in situ, has been seen to fill in a postoperative arteriogram.

In the anastomosis of blood vessels the surgeon is dealing with an unusually difficult group of factors, the most uncertain being the clotting hazard. With the advent of anticoagulants it became possible to neutralize this hazard, but at the same time the danger of bleeding was increased and the balance between these two extremes of too much clotting or too much bleeding is still not easily controlled. In the 31 implantations of grafts reported here, anticoagulants were used in 23 instances. In some cases heparin alone was used, in others it was accompanied by either Dicumarol or Tromexan. Regional heparin was used in four instances. Among those patients receiving anticoagulants the grafts were successful in 11 instances. Failure occurred in 12 of the 23, hematoma formation being present in six of them and considered a factor in the unfavorable outcome. Of the 16 successful grafts, anticoagulants were used in 11 cases. There were no hematomas, though one patient developed a transient hematuria. Of the 15 failures anticoagulants were omitted in only three instances. The types of anticoagulants used and their methods of control must be considered as variables, and it is difficult to appraise the role of anticoagulant drugs in any study. It is still more difficult where a variety of drugs is employed. In our series of cases anticoagulants do not appear to have been an important factor in the success or failure of the grafts.

Summary

1. In 30 patients having segmental blocks in the superficial femoral arteries the obstructed segments have been resected and replaced with venous grafts (bilaterally in one patient). Sixteen of the grafts were successful, 15 failed.

2. The replacements included two femoral vein autografts, 22 saphenous autografts and seven saphenous homografts.

3. Factors possibly contributing to success or failure of the grafts are grouped under two main headings: (a) selection of patients and (b) technical details of surgery. The importance of the proper selection of patients is emphasized, the outstanding contraindication being rest pain and trophic changes in the foot of the extremity under consideration. Arteriography is necessary to the proper selection of patients but may be misleading as well as helpful. Technical details of surgery are important in the outcome and various factors under this heading are discussed.

Sumario Español

Obstrucción de segmentos de las arterias periféricas puede ser causado por arterioesclerosis. Se informa adicional experiencia en la resección de estos segmentos y substitución con injertos de vena. Substitución de segmentos de la arteria femoral se han efectuado en 30 pacientes. La propia selección de los pacientes es esencial para el buen resultado. Las varias causas de fracasos y la limitación del procedimiento se recalcan.

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Clinical Appraisal of a New Adrenergic Blocking Agent: Effect of Regitine on Digital Blood Flow in Normal Subjects and Patients with Peripheral Arterial Diseases

By CHARLES W. CLARKE, JR., M.D., DAVID RANDALL HAYS, JR., M.D., AND THEODORE B. VAN ITALLIE, M.D., WITH THE TECHNICAL ASSISTANCE OF IRENE M. THOMPSON, R.N.

By means of venous occlusion digital plethysmography, the authors have evaluated the peripheral vasodilating effect on normal and diseased arterioles of a new adrenergic blocking agent, Regitine, 2-[-(*m*-Hydroxy-N-*p*-tolylanilino)-methyl]-2-imidazoline. Results have been compared with the results of similar studies using Priscoline and indirect body heating to produce vasodilation. The effect of parenteral Regitine on pulse and blood pressure has been noted as well as the clinical results obtained when this drug was used orally for the treatment of certain forms of peripheral vascular disease.

WITH the frequent appearance of drugs presumed to influence peripheral blood flow, it has become increasingly important to have an objective method of appraising such agents clinically. In a previous paper,[1] two of the authors (T. B. V. I. and C. W. C.) described such a method, based upon studies of digital blood flow as measured by the venous occlusion plethysmograph.

The following report concerns the application of this method to the evaluation of a new adrenergic blocking agent known as Regitine (preparation C-7337). Chemically, this agent is 2-[-(*m*-Hydroxy-N-*p*-tolylanilino)-methyl]-2-imidazoline, a congener of Priscoline and of Privine. Meier and his associates[2, 3] have contributed much of the pharmacologic and toxicologic data on Regitine. More recent studies have been published by Trapold, Warren and Woodbury.[4] In man, Longino, Grimson, Chittum and Metcalf[5] showed that the drug can be administered orally, intramuscularly and intravenously and that it reduces blood pressure, increases cardiac rate, blocks certain vascular reflexes, abolishes the temperature gradient of the extremities, and may produce such side effects as flushing, ptosis of the lids and nasal congestion. Longino and his associates, among others, also noted that in dogs, Regitine blocks the pressor effect of epinephrine. Plummer[6] found that in animals a larger amount (three to five times) of Regitine was needed to reverse the pressor effect of norepinephrine than was required in the case of epinephrine. Walker[7] studied the effect of Regitine on the carotid sinus reflex and on the peripheral vascular actions of epinephrine and norepinephrine and showed clearly that the drug is "adrenolytic" in much smaller doses than are needed to produce a "sympatholytic" response.

As might be expected, clinical interest in Regitine has centered on its use in various disorders of the peripheral circulation and in hypertension, including that variety of hypertension caused by chromaffin tumors. This paper reports our experience with this drug, used in the treatment of peripheral arterial insufficiency.

In 1949, Grimson, Chittum and Longino[8] reported that Regitine might be useful in the treatment of certain disturbances of the peripheral circulation. Using a previously described

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technic,[1] we have carried out studies in which the effect of Regitine on the digital blood flow of normal subjects and patients with peripheral arterial insufficiency was measured by means of venous occlusion plethysmography. The results were then compared with the results of similar plethysmographic studies done on the same normal subjects and patients (with occasional exceptions to be noted) in which Priscoline and later indirect body heating were used to produce peripheral vasodilatation. Indirect body heating is considered by many investigators to be a convenient and yet effective method of relaxing central vasomotor tone. The resulting increase in peripheral blood flow is said to be comparable to that obtained by paravertebral block and spinal anesthesia.[9] The highest value for peripheral blood flow measured after body heating has been referred to as the "maximal flow" for that procedure, and is a useful standard of reference with which the effects of other vasodilating agents can be compared.

A concurrent study was conducted in which orally administered Regitine was used in the long-term therapy of ambulatory clinic patients with peripheral arterial insufficiency.

Plethysmographic Studies

1. Subjects

Blood flow and pulse volume studies were performed on five normal subjects and 19 patients with various types of peripheral arterial insufficiency. Among the 19 patients, there were 29 diseased extremities available for examination. The group of normal subjects was composed of five nurses, all in excellent health, with an average age of 23 years. The group of patients with arterial disease was further subdivided into three categories: (1) patients who displayed predominantly vasospastic disease of the peripheral arteries; (2) patients who had primarily organic peripheral vascular disease; and (3) patients who previously had been subjected to lumbar sympathectomy because of peripheral vascular disease. These groups were established in accordance with the response of the patient to indirect body heating.[1] The patients with vasospastic arterial disorders were four in number, three males and one female, the average age of this group being 35 years. The group exhibiting organic peripheral arterial disease averaged 57 years of age, and was composed of 11 males and two females. The five patients in the postsympathectomy group were all males, and their ages averaged 42 years.

2. Procedure

All subjects visited the Peripheral Vascular Laboratory on at least one occasion, and most of the subjects were examined on three occasions, each separated by two or more days. Examinees were not allowed to smoke, use coffee, tea or liquor, or any drug during the 12 hours preceding examination. Upon arrival at the laboratory, the procedure described in detail in an earlier publication[1] was followed. Briefly, this consisted of placing the patient in bed, allowing a rest period and performing oscillometric and skin temperature determinations in the locations indicated. Plethysmograph cups were then applied to a toe of each foot or, when only one leg was diseased, to a digit of the involved extremity and the left index finger. In the case of the normal subjects, the left great toe was always used together with the left index finger. The material used to seal the cups to the digits was Kalk-Kord,* a nondrying caulking compound.[10]

After rest periods varying from 45 to 90 minutes, the blood pressure and pulse rate were determined and resting blood flow and pulse volume determinations were done. A venous occlusion plethysmograph of the transmission type, constructed on the basis of a principle described by Goetz[11] in 1940 was used. After reproducible resting values for digital circulation had been determined, each subject received an intramuscular injection of Regitine. Persons with peripheral vascular disease received an average dose of 0.75 mg. per kilogram of body weight. Normal subjects received an average dose of 0.6 mg. per kilogram.† The site of injection was uniformly the left deltoid muscle. Plethysmographic tracings were taken at intervals of 5, 10, 20 and 30 minutes following administration of the drug. Blood pressure and pulse rate were measured at the same times, and the patient was observed for untoward effects. Following the last plethysmographic, blood pressure and pulse rate determinations, oscillometric and skin temperature readings again were taken.

With a few exceptions, all the patients returned to the laboratory on two later occasions for comparative plethysmographic studies in which Priscoline and body heating were separately employed for vasodilatation. The procedure followed was similar to the one used for Regitine, except that the dose of Priscoline was always 50 mg. intramuscularly (thus the average patient received between 0.7 and 0.8 mg. per kilogram). When indirect body heating was used, the patient, after the usual period of rest, was asked to submerge his right arm to a few inches above the elbow in water kept at 40 to 45 C. The

* Manufactured by Presstite Engineering Company, 3900 Chouteau Avenue, St. Louis, Mo.

† This smaller dose was instituted after the earlier dose produced severe side effects in two normal subjects.

subject was also covered by blankets to minimize loss of body heat. Plethysmographic studies were done 10, 20 and 30 minutes after the start of body heating.

Results of the plethysmographic studies were corrected[12-13] for variations in digital volume and are expressed in cubic centimeters of pulse volume per 15 cc. of digital tissue, and cubic centimeters of blood flow per minute per 100 cc. of tissue. The essential data obtained by means of these procedures are shown in table 1.*

It will be noted that considerable variation normally occurs in the resting blood flow and pulse volume of normal individuals and patients subjected to repeated plethysmographic study. The averages listed below for the group of normal subjects on three separate occasions are illustrative of this fact. It will be seen, however, that the existence of such variations does not in practice prevent the disclosure either of the relative vasodilating ability of the agents under investigation or of the ability of the vessels of the various groups of subjects studied to dilate in response to the agents.

3. Results

Prior to the administration of Regitine, the average resting digital blood flow of five normal subjects was found to be 9 ± 8.3 cc. (per minute per 100 cc. tissue). The average pulse volume at this time was 0.0058 ± 0.0034 cc. After administration of Regitine, the average maximal blood flow was 27 ± 20.2 cc. and the average maximal pulse volume was 0.0150 ± 0.0049 cc.

Prior to indirect body heating, the average resting blood flow among normal persons was 29 ± 23.9 cc. and the average pulse volume was 0.0106 ± 0.0019 cc. After body heating, the average maximal blood flow among normal subjects was 79 ± 31 cc. and the average pulse volume was 0.0204 ± 0.0035 cc.

Prior to the administration of Priscoline, the average resting blood flow in the group of normal subjects was 11.8 ± 10.5 cc. and the average pulse volume was 0.0058 ± 0.0033 cc. After Priscoline, the average blood flow reached a maximal value of 58.8 ± 19.8 cc. and the average pulse volume increased to 0.0198 ± 0.0016 cc.

Thus, in the normal subjects Regitine produced a threefold increase in blood flow, indirect body heating produced approximately a threefold increase and Priscoline was followed by a fivefold increase. The increases in pulse volume were approximately threefold after Regitine, twofold after body heating, and threefold after Priscoline.

In the patients with vasospastic arterial disorders, the average resting blood flow of the four patients examined prior to administration of Regitine was 2.8 ± 2.9 cc. (per minute per 100 cc. tissue). The average pulse volume at this time was 0.0043 ± 0.0038 cc. After the administration of Regitine, the average blood flow increased to 14 ± 10.2 cc. and the average pulse volume increased to 0.0082 ± 0.0035 cc.

Before indirect heating, these same patients with vasospastic disorders had resting blood flow and pulse volume values averaging 5.3 ± 5.2 cc. and 0.0058 ± 0.0041 cc. respectively. After heating, these values increased to 37 ± 18.7 cc. and 0.0166 ± 0.0070 cc. respectively. Before Priscoline, the group with vasospastic arterial disorders showed an average resting blood flow of 2 ± 0.7 cc. and resting pulse volume of 0.0022 ± 0.0016 cc. After administration of Priscoline intramuscularly, the average blood flow reached a maximal value of 20 ± 6.9 cc. and the average pulse volume reached 0.0138 ± 0.0030 cc.

Thus, in the group of patients with spastic peripheral vascular diseases, Regitine produced a fivefold increase in digital blood flow, indirect body heating produced more than a sevenfold increase and Priscoline was followed by approximately a tenfold increase. The average increases in pulse volume in these patients produced by each agent were respectively twofold, threefold and sixfold.

The thirteen patients with organic occlusive peripheral vascular disease had an average resting blood flow of 11.4 ± 10.5 cc. (per minute per 100 cc. tissue) prior to administration of Regitine. Their average pulse volume at rest was 0.0031 ± 0.0020 cc. After Regitine, the average maximal blood flow increased to 21.7 ± 15.3 cc. and the average pulse volume increased to 0.0046 ± 0.0041 cc.

Because of subsequent amputations or deaths, it was possible to study only 9 of the 13 patients with organic peripheral vascular

* For economy of space, table 1 which presents the raw data is being omitted from the published paper. This table will be furnished on request.

disease by means of indirect body heating and Priscoline. The average resting blood flow for these nine prior to body heating was 14 ± 12.2 cc. (per minute per 100 cc. tissue). The resting pulse volume was 0.0024 ± 0.0030 cc. After body heating, the average maximal blood flow was 24 ± 12.4 cc. and the pulse volume averaged 0.0038 ± 0.0041 cc.

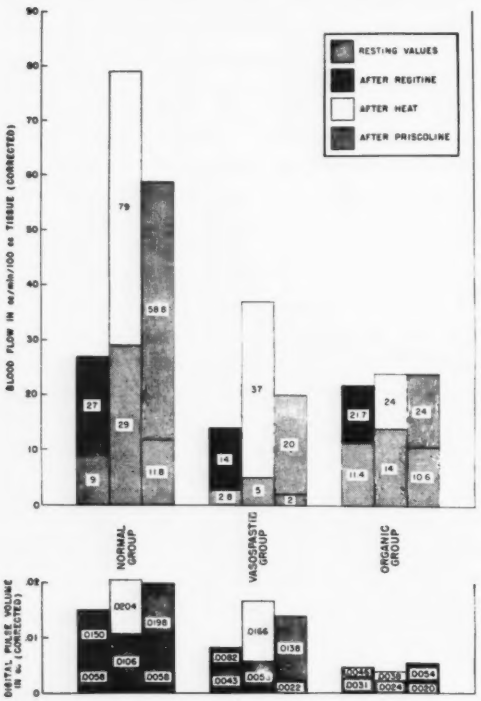

FIG. 1. Comparison of effects of Regitine, Priscoline and indirect body heating on digital blood flow and pulse volume in normal subjects and patients with predominantly spastic or organic peripheral vascular disease (see text).

Prior to injection of Priscoline, the average resting blood flow in the organic peripheral vascular disease group was 10.6 ± 5.6 cc. Pulse volume at this time was 0.0020 ± 0.0019 cc. After administration of Priscoline, the maximal blood flow increased to an average of 24 ± 12.1 cc. and pulse volume increased to 0.0054 ± 0.0049 cc. Therefore, in the group of patients with organic peripheral vascular disease, Regitine produced an increase in digital blood flow which was less than twofold. Indirect body heating also increased blood flow less than twofold, and Priscoline brought about a slightly more than twofold increase. Average increases in pulse volume resulting from the administration of these three agents were also less than twofold in the case of Regitine and body heating and somewhat more than twofold following Priscoline. A graphic comparison of the effects of Regitine, Priscoline and indirect body heating on digital blood flow and pulse volume in normal subjects and patients with vasospastic or organic peripheral vascular disease is shown in figure 1.

In an effort to determine the effect of Regitine upon the sympathectomized limb, five patients who had been subjected to lumbar sympathectomy were studied. In these subjects the average resting digital blood flow prior to administration of Regitine was 15.7 ± 17.6 cc. (per minute per 100 cc. tissue). Pulse volume at this time averaged 0.0028 ± 0.0019 cc. After intramuscular Regitine, the average blood flow *decreased* to 14 ± 12.6 cc. and the average pulse volume *increased* to 0.0045 ± 0.0017 cc. Decreases in blood flow in sympathectomized limbs following the administration of vasodilating agents affecting the entire circulation probably occur as a result of dilatation of the vascular bed elsewhere in the body with subsequent shunting of blood away from the unresponsive limb. This finding has obvious therapeutic corollaries.

EFFECT OF REGITINE ON PULSE AND BLOOD PRESSURE

Regitine has been found to be one of the few adrenergic blocking substances with essentially no cholinergic effect.[5] It differs markedly from Priscoline in this respect. Priscoline is known to produce quite unpredictable changes in pulse rate and blood pressure; moderate decreases to marked increases in each may occur. Regitine, on the other hand, appears to follow a rather definite pattern in its overall effect on cardiovascular dynamics. Generally, it produces a fall in blood pressure and a rise in pulse rate. Our findings were largely in conformity with this pattern, but exceptions in certain individual cases were noted and are described below.

Blood pressures of the five normal subjects averaged 117/72, at rest. When the maximal changes in each subject after the administration of Regitine were averaged, a figure of 109/61 was obtained. The maximal fall (of four cases) was from 130/80 to 108/64 and the maximal increase (one case) was from 114/60 to 130/60.

A similar hypotensive response occurred in the patients with peripheral vascular diseases. The resting blood pressures of all 19 patients averaged 142/89. Following intramuscular Regitine, the blood pressure in persons with peripheral vascular disease fell to an average of 135/84. In this group, seven patients had rises in blood pressure after Regitine; the remainder had varying degrees of fall in blood pressure. The maximal fall was from 164/104 to 128/90, and the greatest rise was from 126/60 to 170/90.

The average resting pulse rate among the five normal subjects was 76 beats per minute. All normal subjects exhibited a rise in pulse rate after intramuscular Regitine. When the greatest increment in each case was used, the average pulse rate after the drug was found to be 86. The greatest individual increase was from 68 to 84.

Among patients with peripheral vascular disease, the average resting pulse rate was 77. Again, in terms of the greatest change after Regitine in each case, the average pulse rate after the drug proved to be 91. Three patients showed no change in cardiac rate as a result of Regitine. The remaining 16 showed varying increases; the largest increase was from 76 to 120 and the least from 70 to 72.

In the 24 persons studied, the following side effects were observed within 30 minutes after injection of the drug: nasal congestion in 14 patients, conjunctival injection in 12, tachycardia in 10, flushing in 8, diaphoresis, piloerection and chills in 3 each, complaints of precordial constriction and anxiety in 2, and nausea in 1 case. Ptosis of the lids was noted rarely. An unexpected side effect observed in a majority of subjects was local pain and tenderness at the site of injection. This sometimes lasted 7 to 10 days, and was undoubtedly due to local irritation of the tissues by the injected substance.

Clinical Observations on the Outpatient Treatment of Peripheral Vascular Disease with Oral Regitine

Many of the patients studied plethysmographically were given a trial on oral Regitine and followed in the Peripheral Vascular Clinic. The results of this study are of interest, but cannot be regarded as conclusive since use of adequate controls was not possible.

1. Procedure

Of the 18 patients studied, 6 were females and 12 were males. Their ages ranged from 19 to 74 and averaged 56 years. Fifteen of the patients suffered from organic peripheral vascular disease and three had some form of vasospastic disorder of the peripheral arteries. The specific diagnosis and a summary of relevant clinical information in each case are in table 2.

History and physical examination of these subjects revealed that of the 18, 11 suffered from intermittent claudication, 10 had night cramps of the legs and 16 reported less specific pains in the lower extremities, which were believed by the examiners to be due to arterial insufficiency. Thirteen complained of chronically cold extremities, seven had discoloration of the involved limbs, five displayed trophic changes of the skin and nails or had outright ulceration, and 15 had absent pulsations of the popliteal, dorsalis pedis or posterior tibial arteries, or all three. Seventeen of these patients had abnormally low oscillometric readings in the involved extremities.

During the period of therapy with Regitine, all other drugs with vasodilating properties were discontinued. However, some of these patients were allowed to continue leg exercises and to use heat and massage as part of a previously established therapeutic program.

Because of sensitivity to Priscoline, three persons were started on 60 mg. of Regitine three times per day. Most of the others received 60 mg. five times per day. One patient tolerated 120 mg. three times per day and another was given 120 mg. five times per day. The average dose was approximately 300 mg. per day. Duration of treatment varied from one day to nine months. Average duration of treatment was 44 days.

2. Results

During therapy with Regitine, 6 of the 11 patients with intermittent claudication reported improvement, 7 of the 10 patients

TABLE 2.—*Summary of Diagnoses, Clinical Findings and Results Obtained in Each of Eighteen Patients Administered Regitine Orally*

Name, Sex	Age	Diagnosis	Aver. Dose	Dur. Treat.	Clinical findings before Reg.							Clinical findings after Reg							Side Effects					Comment
					Claudication	Cramps	Pain	Cold	Poor Color	Trophic Change	Pulses Absent	Claudication	Cramps	Pain	Cold	Poor Color	Trophic Change	Pulses Absent	Nausea, Vomit.	Diarrhea	Chills	Dizzy, Faint	Miscellaneous	
E. B. (M)	62	Arteriosclerotic peripheral vascular disease	60 mg., 5.i.d.	1 month	+	+	+	0	0	0	+	+	+	+	0	0	0	+	0	+	0	0	*	No benefit
R. B. (M)	70	Arteriosclerotic peripheral vascular disease	60 mg., t.i.d.	1 week	+	+	+	+	+	+	+	0	0	0	+	+	+	+	0	+	0	+	†	Drug stopped because of extrasystoles
J. C. (M)	46	Arteriosclerotic peripheral vascular disease	60 mg., 4.i.d.	1 week	0	0	+	+	+	0	0	0	0	+	+	+	0	0	0	0	0	0	F	No benefit. Drug stopped because of palpitations
L. D. (M)	60	Thromboangiitis obliterans	60 mg., 5.i.d.	2 weeks	0	0	+	+	+	0	+	0	0	+	+	+	0	+	+	+	0	0	‡	No benefit. Drug stopped because of G.I. disturb.
E. E. (M)	74	Arteriosclerotic peripheral vascular disease	60 mg., 5.i.d.	1 month	0	0	+	0	0	0	+	0	0	0	0	0	0	+	0	+	0	+	§	Some benefit. Drug stopped because of fainting
H. F. (M)	52	Thromboangiitis obliterans	120 mg., t.i.d.	3 weeks	+	+	+	+	+	0	+	+	+	+	+	+	0	+	+	+	0	0	0	No benefit
M. K. (F)	52	Scleroderma	60 mg., 5.i.d.	1 month	0	0	0	+	+	+	0	0	0	0	+	+	+	0	0	0	+	+	*‡	No benefit
F. K. (F)	64	Arteriosclerotic peripheral vascular disease	60 mg., 5.i.d.	2 months	+	0	+	0	0	0	+	+	0	+	0	0	0	+	0	0	0	0	0	No benefit
R. L. (F)	68	Arteriosclerotic peripheral vascular disease	60 mg., t.i.d.	6 months	+	+	+	+	+	0	+	0	0	0	0	0	0	+	0	0	0	0	0	Relieved of symptoms
R. F. (M)	61	Arteriosclerotic peripheral vascular disease	60 mg., 5.i.d.	1 week	+	+	+	+	0	0	+	+	+	+	+	0	0	+	+	+	+	+	*	No benefit. Could not tolerate drug
L. S. (F)	45	Arteriosclerotic peripheral vascular disease	60 mg., 5.i.d.	2 months	+	+	+	+	0	0	+	0	0	0	+	0	0	+	0	0	0	0	0	Relieved of symptoms
E. M. (M)	52	Arteriosclerotic peripheral vascular disease	60 mg., t.i.d.	1 month	0	+	+	0	0	0	+	0	0	0	0	0	0	+	0	0	0	0	0	Subjective improvement
D. S. (M)	28	Diabetic peripheral vascular disease	60 mg., 5.i.d.	1 month	0	0	0	+	0	+	0	0	0	0	+	0	+	0	0	0	0	0	0	No benefit
J. H. (M)	72	Arteriosclerotic peripheral vascular disease	60 mg., 4.i.d.	1 month	+	+	+	+	0	0	+	0	0	0	+	0	0	+	0	+	0	0	0	Subjective benefit
E. W. (M)	19	Thromboangiitis obliterans	120 mg., 5.i.d.	9 months	+	+	+	+	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	Improved
J. H. (M)	59	Diabetic peripheral vascular disease	60 mg., 5.i.d.	1 month	+	+	+	+	0	0	+	0	0	0	0	0	0	+	+	+	0	0	*	Some benefit. Stopped because of diarrhea
E. S. (M)	2	Diabetic peripheral vascular disease	60 mg., 5.i.d.	1 day	+	0	+	+	+	+	+	+	0	+	+	+	+	+	0	+	0	0	0	No benefit. Stopped because of diarrhea
A. D. (F)	60	Diabetic peripheral vascular disease	60 mg., 5.i.d.	1 month	0	0	+	0	0	+	+	0	0	0	0	0	0	+	+	+	0	0	0	Moderate benefit

+ = Present; 0 = Absent; * = Tachycardia; † = Extrasystoles; F = Palpitation; ‡ = Anorexia; § = Fainting.

with cramps had varying degrees of relief, and 9 of the 16 subjects with poorly localized pain experienced improvement. However, only 3 of 13 patients with cold extremities described relief of this symptom, 1 of the 7 patients with discoloration showed improvement, 1 of the 5 persons with trophic changes obtained benefit, and 1 of the 15 patients with absent peripheral pulses developed a palpable dorsalis pedis. Oscillometric studies done at intervals during treatment showed increases in only one case (E. W.).

Regitine by mouth produced toxic side effects in 11 of the 18 patients. Five patients developed nausea and/or vomiting, two had chills, four complained of dizziness or faintness, four had tachycardia and two developed anorexia. Precordial pain, diaphoresis and extra systoles occurred once, each in a different patient. By far the most frequent and most troublesome toxic effect of oral Regitine was diarrhea. Ten persons developed this symptom and diarrhea was a factor in forcing discontinuance of the drug in five instances. Several persons were given tincture of belladonna by mouth in an effort to block this effect of Regitine; however, only one improved and this person only temporarily. This finding supports the contention that Regitine is without cholinergic effect. The diarrhea probably occurred as a result of direct irritation of the intestinal mucosa.

The size of the dose seemed to have little to do with the occurrence of toxic side effects. This was particularly true with respect to the diarrhea. Thus, one patient developed loose stools after the first few doses of the drug; another person received 120 mg. five times per day for over nine months and showed no toxic effect whatever.

Of the 18 patients given oral Regitine, 9 reported no benefit from the drug and of these, 5 had diarrhea. Of the remaining nine who did benefit, one finally had to stop the drug because of severe diarrhea, one stopped because of numerous extrasystoles and one because of attacks of syncope. Therefore, only 6 of the original 18 patients benefited from oral Regitine and at the same time had either no toxic effects (four) or else side effects of only minimal severity (two).

| | | |

Summary

Studies on the clinical use of a new adrenergic blocking agent known as Regitine or preparation 7337 and chemically as 2-[-(*m*-Hydroxy - N - *p* - tolylanilino) - methyl] - 2 - imidazoline are described. The effect of this drug on digital blood flow was compared with the effect of indirect body heating and of Priscoline by means of venous occlusion digital plethysmography. The effect of Regitine on blood pressure and pulse rate was studied. The long term oral use of this drug in patients with peripheral vascular disease also was studied. The data obtained support the following conclusions:

1. Intramuscular Regitine is somewhat inferior to Priscoline in its ability to increase digital blood flow over resting values in normal subjects and patients with peripheral vascular diseases.

2. Intramuscular Regitine provokes side effects such as nasal and conjunctival congestion, tachycardia, and flushing. It also has a local irritative effect at the site of injection. Generally, administration of the drug is followed by a decrease in blood pressure and acceleration of the pulse rate.

3. Administered by mouth to persons with peripheral vascular diseases, Regitine is found to be of benefit in only a small percentage of cases. A variety of side effects occur, the most severe and common of which is diarrhea.

4. The importance of having an objective method for appraising the effect of new drugs on peripheral blood flow in man is stressed.

Sumario Español

Por medio de pletismografía de oclusión digital venosa, los autores han evaluado el efecto vasodilatador periférico en arteriolas normales y patológicas de un nuevo agente bloqueador adrenérgico, Regitine, 2-[-(*m*-Hydroxy-N-*p*-tolylanilino)-methyl]-2-imidazoline. Los resultados han sido comparados con los resultados de similares estudios usando Priscolina y calor indirecto al cuerpo para producir vasodilatación. El efecto del Regitine parentérico en el pulso y presión arterial fué observado asi como los resultados clínicos obtenidos cuando la droga se usó oralmente para el tratamiento de ciertas formas de enfermedad perífero vascular.

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Spontaneous and Induced Variations in Serum Lipoproteins

By H. L. Chandler, M.D., E. Y. Lawry, Ph.D., K. G. Potee, M.D., and G. V. Mann, M.D.

The diurnal variability of several classes of serum lipoproteins and cholesterol has been measured in human subjects. The S_f 12–20 class of lipoprotein and the cholesterol were found stable in reference to the technical limitation of the method, but the S_f 20–100 class showed significant variation although without evidence of a trend. The effect of intravenous heparin treatment was described. The buccal administration of heparin had no effect. The heparinoid substance Treburon produced a decrease in the S_f 20–100 material at three and five hours and decrease in serum total cholesterol and phospholipids at five and seven hours when administered buccally.

THE CONCEPT that atherosclerosis is a progressive metabolic disease is now widely accepted. That lipid metabolism is directly involved in this condition is suggested both by the prominence of fatty constituents in the lesions and the frequency of associated abnormalities of serum lipid concentrations. The significance of the circulating lipids in the pathogenesis of this disease is not established. During the past several years much interest has been evoked by the reports of Gofman and his group suggesting a close relationship between high concentrations of certain ultracentrifugally identified and quantitated low density serum lipoprotein molecules and atherosclerosis.[1,2] Keys, after independent statistical treatment of the same data, has concluded that these specific lipid particles show no greater correlation with atherosclerosis than does the serum cholesterol level.[3] A large scale investigation by several cooperating ultracentrifuge laboratories is in progress to clarify these claims. Whatever the relative merits of these measurements it is apparent that if only one or at most a few measurements of the serum lipids are available, interpretation of such data is dependent upon some knowledge of the variability of the material measured.

The conditions which induce alterations in the serum cholesterol and lipoprotein levels are incompletely known. Most observers have found that restriction of the total lipids of a usual American diet to about 50 Gm. per day has led to a reduction of the serum cholesterol.[4] Experiments in this laboratory have shown that when individuals are placed on such a low fat diet and are at the same time placed in negative caloric balance both the serum cholesterol and all classes of lipoproteins studied were sometimes lowered.[5] The serum lipid changes were restricted to those subjects with initially elevated levels; for example, with cholesterol greater than 300 mg. per 100 cc. and S_f 12–20 greater than 59 mg. per 100 cc. Another experiment revealed significant increases in both the serum cholesterol and lipoprotein content of serum when normal young males were placed in strong positive caloric balance with a fat free diet.[5] It appeared that changes could be induced in these serum lipids either by reducing the dietary fat or by altering caloric balance. Experimental work in animals and human subjects done in this laboratory indicated that the serum cholesterol is sensitive to physiologic stress.[6] It was found that such agents as cold, fever, and inanition lowered the serum cholesterol. It was then demonstrated that corticotropin (ACTH) would produce the same effect although cortisone was shown not to be the effective adrenal steroid mediating this action. These experimental observations are supported by the finding that the serum cholesterol and the S_f 12–100 classes of lipoproteins are transiently lowered following a myocardial infarction.[7]

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The use of thyroid extract in patients with hypothyroidism is well known to lower serum cholesterol levels, and in a small group of such patients it has been reported to lower the levels of serum S_f 12–20 lipoproteins.[8] Heparin, administered intravenously or intramuscularly, has been shown to result in a sharp decrease in the serum lipoproteins but to have little or no effect on the serum cholesterol.[9]

It has been stated by Gofman and his co-workers[2] that in individuals on a steady diet and without specific therapy there is a "reasonably stable level of concentration" of molecules of the S_f 12–20 group, regardless of whether the concentration is low or high, or whether the analysis is performed on blood drawn in the fasting state or during alimentary lipemia. This conclusion was based on a second measurement two days to three months after the first measurement on 65 individuals. The measurements were made on blood drawn at any time of day and without particular reference to meals. In a subsequent communication from the same laboratory the standard error of any single obtained value was defined as 15 mg. per 100 cc. for S_f 12–20 lipoproteins and 29 mg. per 100 cc. for cholesterol.[10] This statement was derived from unpublished data consisting of determinations repeated on the same individual within a one-year period. We have found no reported data dealing with spontaneous changes in concentration of these lipoproteins within a 24-hour period.

The studies described here were designed to define the spontaneous diurnal variations in these classes of lipoprotein and cholesterol. Such data then provided a frame of reference for measurement of the acute effects of various agents in altering the concentrations of lipoprotein classes and cholesterol in the serum. Another complementary study will be published which deals with the spontaneous variability of these quantities over a 10-week period.[11]

Methods

Venous blood was used in all determinations. For cholesterol and lipoprotein analyses serum was obtained by permitting drawn blood to clot at room temperature for about two hours. This was then centrifuged and the serum separated and stored at 0 to 5 C. for not more than four days until the laboratory measurements were performed. Clotting times were done at room temperature by a modified Lee-White technic with two 8 mm tubes and using 1.0 cc. of blood from the total 25 to 30 cc. drawn.[12] There was undoubtedly some error introduced because of turbulence, but the data have relative value. Serum lipoproteins of the S_f 12–20, 20–100 classes were measured by the method of Gofman and his associates[1]; when analyses were made in duplicate the mean value was used. Serum cholesterol was determined by the technic of Abell and co-workers.[13] Fresh serum was used in the measurement of phospholipids by the procedure of Schmidt and associates.[14]

Diurnal Variations of Lipoproteins and Cholesterol

Three female and five male hospitalized patients, ranging in age from 41 to 72 years and one healthy, young male were bled before breakfast, before lunch, before or after dinner, and again before breakfast on the second day for lipoprotein and cholesterol analyses. Five male and four female healthy young adults ranging in age from 21 to 28 were bled before each of the three meals of one day for lipoprotein, cholesterol, and phospholipid determinations.

Table 1 shows the daily means and standard deviations for each of these 17 subjects, the diurnal variations for the healthy and hospitalized groups and the pooled diurnal variation for the entire series. The variation of the lipoproteins of the hospitalized group appears greater than that of the healthy group; the difference is not statistically significant for the S_f 20–100 class of lipoproteins and is barely significant at the 5 per cent level for the S_f 12–20 class. The variabilities of the serum lipids of the two groups of subjects may differ because of difference in state of health, but age and initial levels are more likely factors contributing to the difference. It was anticipated that the older group with higher initial levels would show greater variability since the error of measurement increases with increases in the concentration being measured, and variability studies extending over a longer period of time show that biologic variation (variability corrected for measurement error) also increases with level.[11] In the present series the effects of these two sources of variability could not be separated. The data of table 1 suggested that

TABLE 1.—*Diurnal Variations of Serum Lipoproteins, Cholesterol and Phospholipids*
(All values in mg. per 100 cc.)

	n	S_f 12-20		S_f 20-100		Cholesterol		Age	Sex	Diagnosis
		Mean	S.D.	Mean	S.D.	Mean	S.D.			
					Hospital Group					
1	4	92	8.5	138	28.2	239	13.0	65	F	Transverse colostomy 2 weeks before for diverticulitis
2	4	75*	4.2	110	32.4	344	27.3	52	M	Myocardial infarction 10 days before
3	4	30	3.4	27	6.3	211	5.0	72	M	ASHD with mild chronic decompensation
4	4	30	5.6	30	5.2	180	9.5	69	F	Diabetes mellitus, gangrene right great toe
5	4	29	5.4	66	15.5	201	6.9	42	M	Alcoholism. No apparent hepatitis. Dietary adequate for at least 3 weeks
6	4	19*	4.4	21	11.9	196	2.8	66	M	Prostatectomy 2 weeks before for B.P.H. On testosterone
7	4	16*	8.5	13	6.4	139	16.1	41	M	Emphysema with cor pulmonale; cardiac failure
8	4	15*	4.0	13	5.8	321	25.7	72	F	Resolving pneumonia
Pooled Variation, Hospital Group			5.8		17.2		15.8			
					Healthy Group					
										Phospholipids
										Mean / S.D.
9	3	29	3.5	35	16.2	172	4.6	28	F	108 / 18.3
10	3	28	1.0	69	14.6	170	3.7	28	M	141 / 4.0
11	3	27	4.6	22	6.1	251	10.8	21	F	121 / 10.6
12	3	24	4.0	55	3.2	205	9.9	24	M	169 / 12.8
13	3	22	6.5	30	17.0	193	1.7	29	F	117 / 4.0
14	4	19	4.3	40	13.9	217	23.2	33	M	
15	3	19	2.5	28	10.1	161	1.2	24	F	123 / 11.0
16	3	18	1.0	12	10.7	200	4.2	25	M	112 / 1.7
17	3	13	4.7	27	12.2	175	5.6	24	M	118 / 4.8
Pooled Variation, Healthy Group			4.0		12.4		10.8			
					(Both Groups)					
Pooled Diurnal Variation:			5.1		15.3		13.8			
Technical Error of Measurement			4.2†		8.4†		14.5‡			

n = Number of bleedings within 24-hour period.
* Bled after, rather than before, evening meal.
† Based on 125 pairs of duplicates. ‡ 98 pairs.

$$\text{S.E.} = \sqrt{\frac{\Sigma\Delta^2}{2R}}$$ in which Δ = difference between duplicates; R = number of pairs.

the standard deviation increased with the mean value, and this may well have been great enough to explain any difference between the two groups. In the pooled data for the entire group the distribution of lipoprotein and cholesterol levels among these persons was comparable to that among the subjects used in the other studies to be described.

The above discussion also applied to the variability of serum cholesterol, with the dif-

ference that the variability for the hospital group was significantly different from that for the healthy group *if* the data for two hospital subjects with levels above 300 mg. per 100 cc. were included, but not significantly greater if these two were excluded. The effect of level on variability was here more conspicuous.

The standard deviations for the S_f 12–20 and total cholesterol measurements computed from the combined data of all 17 persons did not differ significantly from the corresponding standard errors of measurement. Greater variation was observed in the S_f 20–100 lipoproteins than could be attributed to technical error alone. This confirmed reports that this class of lipoprotein was more variable than was the S_f 12–20 class. These measurements revealed no trends in either class of lipoproteins or in the cholesterol throughout the day.

Two subjects, 1 and 7, showed variations in the S_f 12–20 class significantly greater than the technical error. Subject 7 may be rejected as perhaps due to error since none of the measurements were in duplicate. All the measurements on subject 1 were made in duplicate, however, and an analysis of variance of these data showed a significant difference between measurements on sera drawn at different times. This emphasized the fact that although the diurnal variation for most individuals or for a group may not exceed the standard error of measurement, it may for some persons, especially those with elevated levels. This possibility, along with the significant variations in the S_f 20–100 class of lipoproteins, indicated that the variations observed in a group of subjects after any treatment should be compared with the variations observed in the same or a control group observed over a comparable period of time, and not solely with the standard error of measurement derived from consideration of duplicate analyses of samples; moreover, the distribution of initial levels in a control group must be similar to that of the treated group in order to make such comparisons valid.

Heparin Effect

Following the allegation of a highly positive correlation between increased levels of serum S_f 12–20 and 20–100 classes of lipoproteins with atherosclerosis, attempts have been made to reduce these serum lipid levels by dietary and pharmacologic means with the hope that the atherosclerotic process would be halted. On the basis of Hahn's observation that heparin clears the lactescence of lipemic serum, this agent was studied for its effect on the serum lipoproteins.[9] A marked alteration of the lipoprotein constitution of serum was described in general terms, but adequate specific data regarding this effect was lacking in the published reports. Such data have been sought in the present study.

Immediately after blood for analysis had been drawn from each of 10 hospitalized patients, 50 mg. of heparin* was administered intravenously to each subject. Three successive blood samples were then secured from each patient according to one of several overlapping time schedules. In this way observations of the effect of heparin in the several subjects were obtained at six different times after the heparin treatment without excessive bleeding of any single subject.

The data were analyzed by comparing the changes induced in the serum lipoproteins and cholesterol levels by the heparin treatment with the changes observed over a comparable period of time in those subjects studied for diurnal variation, described above. For each individual the difference between his own control measurement and that observed at a given time after treatment was obtained. The mean of these differences for the treated subjects was then compared with the mean difference obtained in a similar manner from those untreated subjects of the diurnal variation study who were observed after the time interval nearest to that under consideration in the heparin study. The range of the S_f 12–20 control levels for the heparin-treated subjects was 18 to 64 mg. per 100 cc.; for S_f 20–100, 13 to 103 mg. per 100 cc.; for cholesterol, 145 to 249 mg. per cent. These ranges were similar to those of the untreated subjects, as table 1 suggests.

The comparisons of the mean changes after heparin treatment with those of the untreated

* The heparin used in this study was supplied by the Upjohn Company through the courtesy of Dr. Joseph Webb.

controls are shown in table 2. The significant changes observed were a decrease in the S_f 20–100 class of lipoproteins 20 minutes after heparin treatment and a decrease in the S_f 12–20 group six hours after treatment. By six hours after heparin the S_f 20–100 class was back to the control level, and by 12 hours after treatment the mean of S_f 12–20 group had returned to the original level. Observations 18 and 24 hours after treatment showed no changes in either quantity. No appreciable variations were observed in the serum cholesterol at any time.

This observation that changes in the S_f 20–100 class preceded those in the S_f 12–20 parallels the experience of Graham and co-workers,[9] and is consistent with their hypothesis that the lipoproteins are converted into progressively smaller molecules of higher density and lower flotation rate. This process, assumed to be a normal and continual aspect of fat transport and metabolism, is accelerated by heparin. From this point of view we can examine these data in greater detail. At 20 minutes after heparin injection the S_f 20–100 levels of all five subjects examined had dropped to values of less than or equal to 12 mg. per 100 cc., which is the limit of resolution of these molecules by our method; that is, all five subjects had S_f 20–100 levels too low to be measured accurately. Three of these persons, all with control S_f 20–100 levels less than 45 mg. per 100 cc., showed decreases of 10 mg. per 100 cc. or more in their S_f 12–20 levels at 20 minutes, while the other two, who showed no change in their S_f 12–20 levels, had S_f 20–100 control levels above 45 mg. per 100 cc. If the rate at which the larger S_f 20–100 molecules are transformed to the smaller S_f 12–20 lipoproteins is roughly the same for most individuals, more time would be required to clear the S_f 12–100 groups of lipoproteins in those persons with higher initial levels; this may be a partial explanation for the differing individual responses at 20 minutes after heparin. Furthermore, if the heparin effect is progressive from the higher S_f classes toward the lower, then the concentration of the S_f 12–20 at a given time must be dependent upon the movement of material to this class from higher classes. This suggests that the action of heparin on these lipoproteins is a selective and sequential one proceeding from less dense to more dense materials in a wave-like manner.

TABLE 2.—*Average Changes in Serum Lipoproteins and Cholesterol in Subjects Treated with 50 mg. Heparin Intravenously Compared with Untreated Control Subjects*
(Mean changes in mg. per 100 cc.)

Time	n	Sf 12–20	Sf 20–100	Cholesterol
20 min. after heparin	5	−13.2 } $p > .05$	−42.8 } $p < .01$	0.0
3 hr. controls*	8	− 0.5	− 1.1	−0.3
6 hr. after heparin	8	−12.1 } $p < .01$	− 7.5 } $p > 0.2$	+2.0
6 hr. controls	8	+ 1.6	+ 2.4	−2.9
12 hr. after heparin	9	− 3.1	+14.4	−5.1
12 hr. controls	9	− 1.5	+ 2.2	−5.0

n = number of observations.
p = probability that the observed difference is due to chance as calculated by Student's "t" test.
* Controls, untreated, taken from diurnal variation study.

Heparin significantly reduced the concentration of the S_f 12–100 lipoproteins, but within a matter of hours the concentration of these molecules had returned to control levels. Perhaps the sequence of events by which the control levels are re-established after heparin treatment is the same as that occurring in the usual process of metabolism. The hypothesis states that these lipoproteins enter into the serum as large molecules and are broken down into progressively smaller molecules. If this be

the case, then the concentration of the larger S_f 20–100 lipoproteins would be expected to increase while the level of the smaller S_f 12–20 class was still low. This sequence was observed at six hours after heparin when all but one of the eight persons observed had S_f 20–100 levels which were definitely measurable; i.e., above 12 mg. per 100 cc. This group as a whole showed levels not significantly different from the controls, whereas the S_f 12–20 lipoproteins showed a significant lowering from the control levels. It appears that the lipoproteins of the S_f 20–100 class may be precursors of those in the S_f 12–20 class. All these changes were transitory and had disappeared by the twelfth hour after treatment.

The most prolonged clotting times were observed at 20 minutes after heparin treatment, when the S_f 20–100 lipoproteins showed a significant fall, but the clotting defect had disappeared after six hours, when the S_f 12–20 class was decreased. This experiment gives no information concerning the relation of the induced clotting defect to the period of reduction of lipoproteins. Obviously the clotting disturbance had disappeared before all the lipoprotein alterations induced by heparin were corrected.

*Transmucosal Heparin**

An effort was made to ascertain whether the lipoprotein active factor of heparin could be absorbed transmucosally. After bloods were drawn for control measurements, three patients were each given 250 mg. of heparin in tablet form, placed in the usual position for buccal absorption. Blood specimens were obtained 20 minutes, one hour, and three hours after the midpoint (30 minutes) of tablet disappearance. No alteration in the concentration of any of the groups of lipoproteins, serum cholesterol, or serum phospholipids was demonstrated. Nor was there a significant change in the clotting times of blood drawn at these intervals.

Treburon†

Treburon is a pectic acid derivative with heparin-like properties chemically identified as the sodium salt of sulfated polygalacturonic acid methyl ester methyl glycoside.[15] In animal tests it has been found to have about one-fourth the anticoagulant and antithrombin effects of heparin on a weight basis with both agents administered intravenously. In human subjects 150 mg. of Treburon administered intravenously was about as effective as 50 mg. of heparin.[16] Oral ingestion of a dose of 2.0 Gm. in man and 1.0 Gm. per kilogram of body weight in rabbits did not alter the coagulation time. No toxicity was demonstrated in an initial study of 138 patients given Treburon parenterally in dosages sufficient to render the blood therapeutically hypocoagulable. However, during the course of the present study, Treburon was withdrawn from parenteral use in clinical investigation because of certain undesirable side effects associated with its use.

In this experiment nine hospitalized patients with a variety of illnesses were utilized. Three of these subjects were selected because they were known to have moderately high lipoprotein levels; the other six were unselected. After obtaining blood samples for control purposes, each patient was given two 500 mg. tablets of Treburon, one on each side of the mouth, for transmucosal absorption. Using the midpoint of tablet disappearance as the zero of time, three subsequent blood samples were drawn from each subject according to either of two schedules so that at least three observations were obtained at 20 minutes and one, three, five, and seven hours after treatment.

As in the treatment of the heparin data, the changes from the individual control levels observed at each interval after Treburon treatment were compared with the spontaneous changes observed in the untreated subjects studied for diurnal variations and described above. The results are shown in table 3. No significant changes were observed in the S_f 12–20 class; the S_f 20–100 lipoproteins were

* The tablet form of heparin was provided by the Abbott Laboratories through the courtesy of Dr. L. E. Josselyn.

† Furnished by Hoffmann-La Roche through the courtesy of Dr. Leo A. Pirk.

significantly decreased three and five hours after Treburon. Both the total cholesterol and phospholipids were significantly reduced five and seven hours after Treburon; this reduction could possibly extend beyond seven hours, at which time our last observations were made. No appreciable changes in clotting times were observed.

probably less satisfactorily, the data secured for evaluation should be compared with control data obtained from a group matched for initial levels and studied under similar circumstances.

During a single day there was less stability in the S_f 20–100 class of lipoproteins than in the S_f 12–20 class. The changes observed

TABLE 3.—*The Effects of 1.0 Gm. of Transmucosal Treburon on the Serum Lipoproteins, Cholesterol, and Phospholipids of Human Subjects*

(Average changes in mg. per 100 cc.)

Time	n	Δ 12-20	Δ 20-100	Δ Cholesterol	Δ Phospholipid
20 min. after Treburon	3	+2.7	−12.3	−19.3	− 6.3
		$p > .4$	$p > .2$	$p > .1$	
3 hr. controls*	8	−0.5	− 1.1	− 0.3	− 4.0
1 hr. after Treburon	3	+1.7	−18.3	− 9.3	− 3.3
			$p > .1$		
3 hr. controls	8	−0.5	− 1.1	− 0.3	− 4.0
3 hr. after Treburon	9	+0.6	−18.2	−10.0	− 3.2
			$.02 < p < .05$	$.05 < p < .1$	
3 hr. controls	8	−0.5	− 1.1	− 0.3	− 4.0
5 hr. after Treburon	6	+0.7	−21.8	−21.3	−39.5
			$.02 < p < .05$	$p < .01$	$p < .01$
6 hr. controls	8	+1.6	+ 2.4	− 2.9	− 4.0
7 hr after Treburon	6	+6.3	−21.8	−28.2	−32.3
			$.05 < p < .1$	$p < .01$	$p < .01$
6 hr. controls	8	+1.6	+ 2.4	− 2.9	+ 4.1

n = number of observations.

p = probability that the observed difference is due to chance as obtained by Student's "t" test.

* Controls, untreated, taken from diurnal variation study.

DISCUSSIONS AND CONCLUSIONS

Within the limitations of the present study, a diurnal constancy of serum S_f 12–20 lipoproteins and cholesterol was found. Exceptions to this conclusion were indicated by the presence of high initial levels of one or both of these lipid components. This limitation indicated that if therapeutic trials are to be conducted with subjects or groups which by design or accident have high serum lipid levels then the biologic variability of the group must be measured in suitable preliminary studies in order to assure a valid basis for comparison of the effect of treatment. Alternatively, but throughout the day in both classes of lipoproteins and in cholesterol showed no pattern that might be related to meals or the day's activities.

The striking reduction, reported by Graham and associates[9] in all the measured lipoproteins, without change in cholesterol, as a result of intravenous heparin was confirmed. The degree of decrease and the time required to accomplish this varied in different individuals in the present study. All subjects observed within six hours after treatment with parenteral heparin have demonstrated a response in the same direction. This effect of 50 mg. of heparin injected intravenously had disappeared by six hours

for the S_f 20–100 class of lipoproteins and by 12 hours for the S_f 12–20 class.

Anfinsen and his collaborators[17] have traced the mechanism of this action of heparin to a system involving substances separated mainly with the globulin fractions of plasma, using Cohn's method[18] of fractionation. Graham, by ultracentrifugal methods, also found that the clearing factor fell in the globulin fraction.[9] It is interesting that the cofactor in plasma which is influenced by heparin to strong antithrombin activity is associated mainly with serum albumen.[19] This suggested that the lipoprotein-altering effects of heparin or heparin-like substances may be dissociated from the anticoagulant effect. Should the initial reports of dramatically beneficial results of heparin in clinical atherosclerotic disease[9] be confirmed in subsequent investigation, and attributable to this action on serum lipoproteins, it would be desirable to find a substance with the same lipoprotein effect yet devoid of potential dangers such as hemorrhage and also one that could be taken conveniently by mouth.

The effect on lipoproteins of transmucosally absorbed Treburon was similar to that of parenteral heparin in that the concentration of the S_f 20–100 class of lipoproteins was significantly reduced at three and five hours after treatment. No reduction of the S_f 12–20 class was demonstrated. It is possible that a more prolonged experiment, to 8 or 10 hours, would show such a change. The rate and degree of response with buccal Treburon were much less than with intravenous heparin, suggesting an attenuation of effect as a result of mode of administration, low dosage, or both. On the other hand, the late and moderate response of the S_f 20–100 molecules and the absence of effect on S_f 12–20 lipoproteins together with the novel effect in lowering the serum cholesterol and phospholipid concentrations suggest that an alternative explanation may be applicable. The only pharmacologic agent known to decrease acutely the serum cholesterol is adrenocorticotropic hormone (ACTH), as mentioned previously in the work of Mann and White. It is conceivable that some factor of absorbed Treburon operates through a mechanism related to that of corticotropin or involving release of this substance. Since the majority of the cholesterol and phospholipid content of serum is in materials of density less than that corresponding to a migration rate of S_f 20, it follows that further study of the effects of Treburon probably will reveal changes in the concentrations of other lipoproteins or perhaps in their composition. This probability reemphasizes the importance of a more decisive segregation and description of the atherogenic potentialities of the various classes of serum lipoproteins.

Summary

1. The fluctuations observed in the S_f 12–20 class of lipoproteins and total serum cholesterol levels during 24-hour periods were no greater than those attributable to measurement error alone. No diurnal trends were observed.

2. The diurnal variation observed in the S_f 20–100 class of lipoproteins was greater than could be attributed to technical error, showed no consistent pattern, and tended to increase with higher mean levels.

3. Fifty milligrams of heparin given intravenously resulted in marked reductions in all lipoproteins from S_f 100 through S_f 12 with maximal effect in the S_f 20–100 class within 20 minutes and in the S_f 12–20 class at about six hours. This effect had disappeared by 12 hours after the heparin administration.

4. The effect of heparin on lipoproteins was not accompanied by serum cholesterol changes.

5. Heparin, in dosage of 250 mg. by transmucosal absorption, had no effect on lipoprotein levels, serum cholesterol, or blood clotting times.

6. Treburon, in a dosage of 1.0 Gm. given by buccal absorption, had a definite effect in decreasing serum S_f 20–100 lipoproteins after three and five hours. This effect had decreased but persisted to seven hours.

7. A significant reduction in serum cholesterol and serum phospholipids was observed five and seven hours after administration of transmucosal Treburon.

8. Treburon given under these conditions caused no appreciable changes in blood clotting time.

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SUMARIO ESPAÑOL

La variación diurna de algunos grupos de lipoproteinas del suero y colesterol se ha determinado en sujetos humanos. La clase S_f 12–20 de lipoproteinas y el colesterol se encontraron estables en referencia a la limitación técnica del método, pero la clase S_f 20–100 mostró variación significativa aunque sin evidencia de curso o tendencia. El efecto del tratamiento con heparina intravenosa se describe. La administración de heparina oral fue inefectiva. La substancia heparinoide Treburon produjo un decremento en el material S_f 20–100 a las tres y cinco horas y un decremento en colesterol total del suero y fosfolipina a las cinco y siete horas cuando se administró oralmente.

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Studies of Human Peripheral Blood Flow: The Effect of Injection Volume on the Intramuscular Radiosodium Clearance Rate

By George F. Warner, M.D., Ernest L. Dobson, Ph.D., Nello Pace, Ph.D., Muriel E. Johnston, M.A., and Caroline R. Finney, A.B.

The effects of changes in injection volume on the intramuscular radiosodium clearance rate was investigated in six normal young men. The clearance rate was found to be quite sensitive to the volume of solution injected, and an increase in the rate of clearance corresponding to a decrease in volume was uniformly noted. Rigid control of the injection volume is necessary when this method is used for regional blood flow measurements.

THE development of practical methods of measuring regional blood flow has been the aim of a number of investigators, particularly since the use of isotopic tracer technics has become more widespread. The work in this field has been ably reviewed by Wright[1] and by McGirr.[2] In general, the approaches to a study of peripheral and/or regional blood flow have taken two principal pathways.

The first general method consists of the measurement of the build-up of activity at a given site following the intravenous injection of a radio-isotope. Smith and Quimby[3] have pioneered this method, employing sodium[24] as the isotope, and have used it extensively in the study of peripheral vascular disorders. Others,[4, 5] however, have questioned the sensitivity of the method. From our own observations, this lack of sensitivity may be due in part to the complications caused by the distributive events occurring elsewhere in the body after intravenous injection of radiosodium.[24]

The second principal method of approach in the study of regional blood flow consists of the measurement of the rate of disappearance of a radioisotope following its local injection, as proposed by Kety.[6] The clearance rate obtained by this method reflects some function of the circulation, because experimental alteration of blood flow produces the expected changes in clearance rate. The rate of clearance is slowed by the application of a tourniquet[7, 8] and by the local injection of adrenaline.[7] The clearance rate is increased by exercise,[7, 9] by reactive hyperemia,[2, 7] by hyperthyroidism,[4] and by the local injection of histamine.[2]

When the intramuscular clearance method has been applied to the study of peripheral vascular disease, overlapping values and lack of sensitivity have also been noted.[2] As reported herein, our own observations with this method have shown that the clearance rate following intramuscular injection is very sensitive to the volume of solution injected. Rigid control and standardization of the injection volume is of utmost importance when this test is applied to a study of regional blood flow.

Methods

Young normal males between the ages of 20 and 30 years were placed in a prone position and isotonic sodium chloride labeled with approximately 5 microcuries of radiosodium[24] was injected intramuscularly with a 23 gage needle at comparable sites and depths of both right and left muscles, usually the gastrocnemius but occasionally the gluteus maximus. A standard 1.0 ml. volume was always injected on one side, and volumes varying from 0.005 ml. to 1.0 ml., but containing the same amount of radioactivity, were injected on the opposite side. Immediately after injection, shielded external counters were used to record the activity remaining at the injection sites.

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Prior to these bilateral injections it was established, with detectors on both extremities and with radiosodium injected on only one side, that dilution of the sodium[24] which enters the circulation from the injected side was so great that no appreciable background effect was noted by the counter over the opposite extremity.

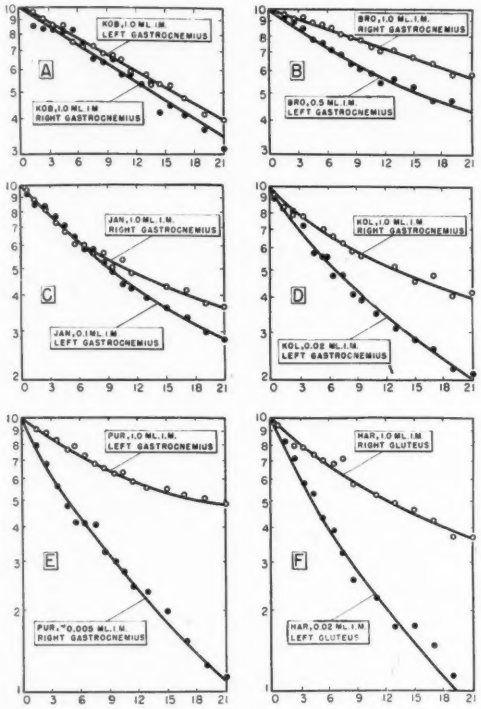
KOB, 1.0 ML. I.M. LEFT GASTROCNEMIUS
A
KOB, 1.0 ML. I.M. RIGHT GASTROCNEMIUS
BRO, 1.0 ML. I.M. RIGHT GASTROCNEMIUS
B
BRO, 0.5 ML. I.M. LEFT GASTROCNEMIUS
JAN, 1.0 ML. I.M. RIGHT GASTROCNEMIUS
C
JAN, 0.1 ML. I.M. LEFT GASTROCNEMIUS
KOL, 1.0 ML. I.M. RIGHT GASTROCNEMIUS
D
KOL, 0.02 ML. I.M. LEFT GASTROCNEMIUS
PUR, 1.0 ML. I.M. LEFT GASTROCNEMIUS
E
PUR, "0.005 ML. I.M. RIGHT GASTROCNEMIUS
HAR, 1.0 ML. I.M. RIGHT GLUTEUS
F
HAR, 0.02 ML. I.M. LEFT GLUTEUS

FIG. 1. Changes in intramuscular radiosodium clearance rates produced by varying injection volumes in six normal young men. Ordinates are normalized activities in counts per minute. Abscissas are expressed as minutes following injection. The initials of the subject and the volume and site of injection are indicated on each graph.

RESULTS

In six subjects so determined, a discrepancy in the rate of clearance corresponding to an alteration in volume was uniformly noted as illustrated in figure 1. The rate of disappearance of the standard 1.0 ml. injection in different individuals showed moderate variation, but when smaller volumes were injected in the same individual, a consistent increase in the disappearance rates was produced whose magnitude was dependent on the smallness of the volume injected. However, when identical volumes were used in the same individual, the clearance rates were practically identical (figure 1).

So that data from all subjects could be studied, the time necessary for the curves to fall to 50 per cent of their initial activity has been used as the basis of comparison. Figure 2 summarizes the data obtained in the six subjects, and demonstrates the correlation

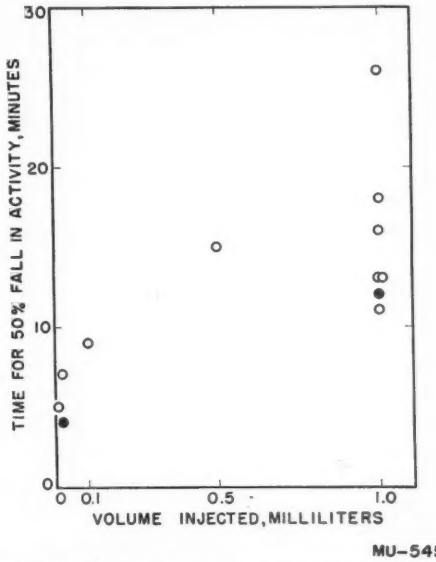

FIG. 2. Scatter diagram summarizing the data in figure 1 and showing the decrease in the time required for a 50 per cent fall in activity caused by decreasing the injection volume. The solid circles represent data obtained from gluteal injections (fig. 1*F*).

between the removal rate and the size of the injection volume for the group as a whole.

DISCUSSION

Presently available data do not completely establish the cause of the variation in clearance rates observed with varying injection volumes. However, several possible mechanisms may be involved either singly or in combination. Among these is the mechanical compression of adjacent capillary beds by a large injection volume. This might be expected to lead to a progressive increase in clearance rate as the

compressing volume decreases with time; however, such a rate change is not observed.

The total quantity of electrolyte which must be removed by a relatively limited capillary bed may be pertinent. In this regard, because of the lack of proportionality between increases in surface area with increases in volume, slower clearance rates with larger injection volumes would be expected. Finally, the relatively long diffusion path for sodium from the center of the injection bubble may be a rate-limiting factor.

Summary and Conclusions

1. The effect of changes in injection volume on the intramuscular radiosodium clearance rate was investigated in six normal young men.

2. An increase in the rate of clearance corresponding to a decrease in volume was uniformly noted.

3. Rigid control of the injection volume is indicated when this method is used for regional blood-flow measurements.

Sumario Español

El efecto de cambios en volumen de inyección en la velocidad de disipación del radiosodio intramuscular fué estudiado en seis hombres jovenes. El promedio de disipación se encontró ser muy sensitivo al volumen de solución inyectada y un incremento en la velocidad de disipación correspondiente a un decremento en el volumen se observó uniformemente. Es necesario un control rígido del volumen a inyectarse cuando este método se usa para la determinación de la circulación regional.

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Magnetic Tape Recording Electrocardiograph

By WILLIAM L. PROUDFIT, M.D., AND JOSEPH F. DOBOSY, B.S.

A method of recording the electrocardiogram on magnetic tape is described and possible applications are mentioned.

RECORDING the electrocardiogram for prolonged intervals presents difficulties from the standpoint of economy and convenience. One 200 foot roll of paper for a direct writing instrument is used in 40 minutes of continuous recording at 25 mm. per second, and reviewing this long electrocardiographic record is a cumbersome procedure. A convenient method of recording electrocardiograms and other low frequency phenomena has been developed.

DESCRIPTION OF METHODS

The electrocardiogram is recorded on magnetic tape of the type used in audio recording. The frequencies involved in the electrocardiogram are so low that it is not possible to record directly on magnetic tape. A carrier wave is necessary, and this is modulated by the amplified electrocardiographic impulses. Figure 1 shows a block diagram of the apparatus which has been developed. Details of the circuit will be reported in a separate communication. Figure 2 is a photograph of the instrument. A differential amplifier is employed, which minimizes the effect of 60 cycle interference. A 250 cycle square wave carrier which is amplitude modulated is used. The frequency of the square wave carrier does not limit the frequency of the impulses which may be recorded in the way in which the frequency of a sine wave carrier does. It is possible to record frequencies as high as and higher than the frequency of the carrier. Amplitude modulation is used because the recorded information is distorted less by fluctuations in the speed of the tape than when frequency modulation is employed. The modulated carrier wave is taken off the magnetic tape by the play-back head of the tape recorder, amplified and visualized on a

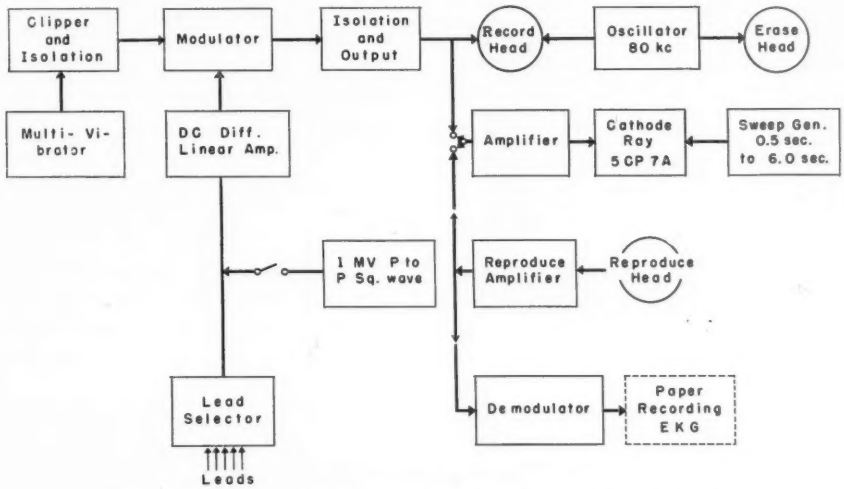

FIG. 1. Block diagram of magnetic tape recording electrocardiograph.

From the Cleveland Clinic and the Frank E. Bunts Educational Institute.

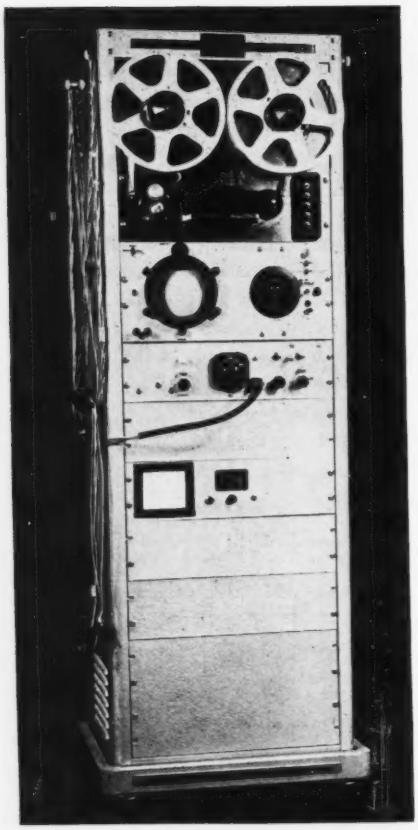

FIG. 2. Magnetic tape recording electrocardiograph.

cathode ray tube either during recording or when reviewed later. The sweep speed of the cathode ray tube is variable, the slowest sweep being six seconds, which makes rapid calculation of the heart rate simple. If more detailed study is required or if a permanent record is desired, the carrier can be rectified and the current picked up by the lead wires of any clinical electrocardiograph. Otherwise the tape is erased and used again. The tape speed during recording is 7.5 inches per second. When the recording is reviewed the tape speed can be 7.5 or 15 inches per second. The more rapid speed enables one to review the record in half the time in which it is recorded. The 10.5 inch reels (2400 feet of tape) run for 64 minutes. Figure 3*A* illustrates an electrocardiogram directly recorded on a string galvanometer, and figure 3*B* is an electrocardiogram from the same patient which was magnetically recorded and played back through the same string galvanometer. Equally satisfactory results are obtained with tape speeds as low as 1.87 inches per second, and at this speed continuous records for more than four hours are possible.

DISCUSSION

The apparatus described has been in clinical use since July 1952. It is employed for continuous recording during anesthesia. It may also prove helpful in certain physiologic in-

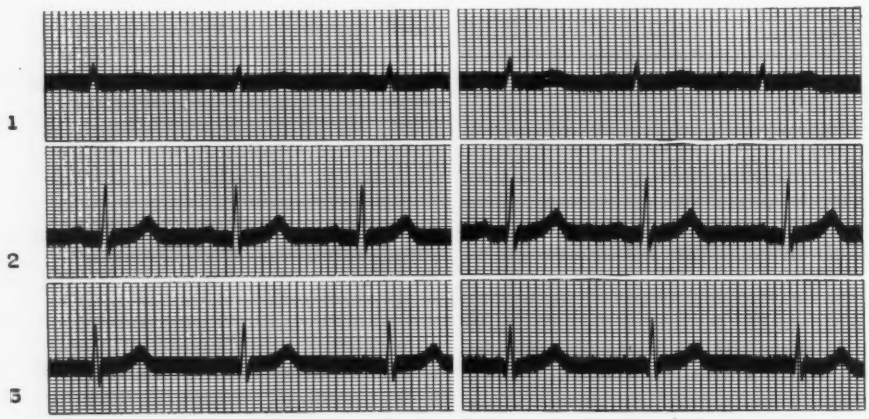

FIG. 3*A*. Electrocardiogram recorded directly on string galvanometer.
B. Electrocardiogram recorded on magnetic tape and played back through string galvanometer.

vestigations, in studying the effect of drugs on cardiac arrhythmias, and in determining the electrocardiographic changes immediately preceding death. Teaching of electrocardiography may be facilitated by the use of this instrument. At present the apparatus is being modified so that voice, heart sounds and other phenomena may be recorded simultaneously with the electrocardiogram.

Summary

A method of magnetic tape recording of the electrocardiogram is presented.

Sumario Español

Un método de registrar el electrocardiograma en cinta magnética se describe y sus posibles aplicaciones se mencionan.

A Ballistocardiographic Study of Healthy Young Adult Males

By WILLIAM B. ABRAMS, 1ST LT., M.C., A.U.S., AND HERBERT D. EDGER, LT. COL., M.C., U.S.A.

Ballistocardiograms were obtained from 319 well-screened young soldiers on an electrically equalized electromagnetic ballistocardiograph. The records were analyzed for the basic pattern and for variations. The conventional criteria of normal were confirmed. The most frequently observed variation consisted of changes in complexes written during expiration which, when of sufficient degree, resemble those described as abnormal. Prominent L waves were also common. Variations of the J and K waves were rare. A grade 1 or 2 abnormality was noted on 22 records, but when respiration was suspended, only three remained questionably abnormal.

IT HAS been established that there is a high degree of correlation between abnormalities of the ballistocardiogram and the presence of heart disease.[1-25] The ballistocardiograph, therefore, has been recommended as a diagnostic tool in the evaluation of the cardiovascular system. In order to define the normal and to test the reliability of the ballistocardiogram as an indicator of heart disease, a number of surveys of apparently normal subjects have been undertaken.[2, 11, 14, 15, 16, 18, 20, 26] In subjects over the age of 40, abnormal records are common. From 10 to 20 per cent of individuals in the fifth decade, 22 to 43 per cent in the sixth decade, and 50 to 90 per cent in the seventh decade and older are reported to have abnormal records. It is suggested that these percentages correspond to the expected incidence of subclinical cardiovascular disease in these older subjects and, therefore, these abnormal tracings may be true records and not variations due to age.[14, 25, 26, 27] It follows that the definition of the normal and normal variations must come from a study of young individuals. The reports indicate that none to 10 per cent of normal subjects under the age of 40 have abnormal ballistocardiograms. Although the ballistocardiographic deflections have been approximated experimentally,[28] the present criteria of normal are largely empiric. There is confusion however, because these criteria have been described for four different types of ballistocardiographs,[2, 27, 29, 30, 31] each of which introduces its own distortions. Recently it has been proposed that the most reliable records are obtained with a displacement (photoelectric) type of direct body pickup.[25, 32] An electromagnetic (velocity) ballistocardiograph will provide a practically identical record if electrically equalized.[25, 32, 33]

It seemed of value, therefore, to obtain ballistocardiograms with such an apparatus from a large group of healthy young subjects. The presence of an Airborne Division at this Post created an opportunity to do this. Records were obtained from 319 of these select soldiers after extensive studies confirmed their good health. Attention was primarily directed to the characteristics of the basic pattern and variations from this pattern as obtained on this simple, inexpensive and accurate instrument.

MATERIALS AND METHODS

The subjects were 319 soldiers mostly from an Airborne Division. A few were post complement personnel. The troops had reported to the Physical Examination Section of this hospital for processing necessary for separation from the service, re-enlistment or eligibility for Airborne training.

The processing consisted of: (1) a complete clinical history, (2) a physical examination, including a blood pressure recording, (3) a chest x-ray study, (4) a serologic test for syphilis and (5) urinalysis. Only individuals in whom these studies were normal were included in the survey. The subjects were of ages 19 through 29 years. The average age was 23.4 years.

The men were directed not to smoke for four hours prior to the test. The recordings were made

From the U. S. Army Hospital, Fort Campbell, Ky.

at least two hours after eating. The cardiovascular system was again reviewed with each subject prior to the test.

The apparatus employed was a Dock model, portable, electromagnetic ballistocardiograph.* Electrical equalization was effected by having a 20 mirofarad capacitor across the coils as recommended by the manufacturer and by Dock.[34] Thus, this electromagnetic transducer of body motion actually writes a displacement curve, has an essentially flat frequency response in the range of the ballistic waves, but attenuates respiratory motion more than if a condensor of larger capacity is used.[25,32,33]

The tracings were recorded on a Cambridge Simpli-Scribe Electrocardiograph with the standardization set at 5 mm. equals 1 mv. A fluoroscopic table provided a solid base. Records were obtained during normal respiration and with the breath held in midrespiration, deep inspiration and deep expiration. Care was taken to avoid an inadvertent Valsalva maneuver.

The ballistocardiograms were analyzed according to the usual criteria as described by Starr,[2] Brown, Hoffman and de Lalla,[13] Dock, Mandelbaum, and Mandelbaum,[14,16,17] Pordy, Taymor, Moser, Chesky and Master,[15] Gubner, Rodstein and Ungerleider,[25] Scarborough, Mason, Davis, Singewald, Baker and Lore[24] and Thompson, Rappaport and Sprague.[35]

Each test was witnessed by one of us (W.B.A.) and if a record appeared to vary from the normal, an electrocardiogram was obtained. Only one abnormal electrocardiogram was obtained and that subject's ballistocardiogram was eliminated from the study.

Results

1. Two hundred and seventy-three of the ballistocardiograms were of the usual basic normal pattern (fig. 1). Each complex consisted, in order, of a low upright H wave, a short, negative I wave that was clearly below the baseline; a prominent positive J wave, the tallest component; a prominent negative K wave, the deepest component; and an upright L wave which was shorter than the J wave but usually taller than the H wave. These waves could easily be identified without a marking system. Essential features of the normal are clean, unslurred lines, sharp acute angles and uniformity of all the complexes.

2. The most frequently observed variation from the basic pattern was that associated with respiration and involved, for the most part, complexes written during expiration. The variation presented itself in a range of degrees. The least degree was noted on a large number of tracings and consisted of a reduction in amplitude with maintenance of form (figs. 1 *D*; 2 *A* and *B*). This is described as a normal finding but in some records the I waves are noted to be disproportionately reduced. Further shortening of the I waves produced high HIJ complexes which made the K waves appear deep (fig. 2 *C*, *D* and *E*). If the L waves of these variant expiratory complexes were also prominent, the "abnormal" high HIJ-deep K-prominent L pattern described by

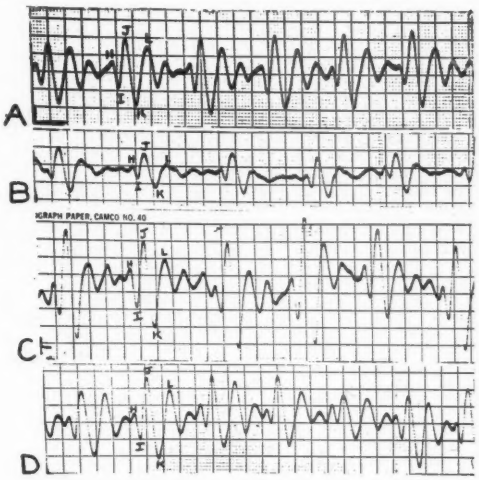

Fig. 1. Typical normal ballistocardiograms. Description in text. These tracings typify the pattern noted in 273 of the 319 records.

Starr[2, 6] and Mandelbaum and Mandelbaum[17] resulted (fig. 2 *F*, *G* and *H*). This type of change is also similar to that described by Brown, Hoffman and de Lalla.[13] This variation was noted on less than half the complexes recorded during normal respiration on 10 records and a grade 1 classification of Brown[13] was therefore assigned (fig. 2 *C*, *D*, *E* and *G*). On five records more than half the complexes were so altered and these were graded 2 (fig. 2 *H* and *F*). In every case normal ballistocardiograms were recorded in one or more of the three positions of held respiration [fig. 2 *C* (2), *D* (2), *F* (2), *G* (2) and *H* (2)].

* Manufactured by the County Surgical Company, Brooklyn, N. Y.

3. On most records there was some weaving of the base line due to respiratory motion. This rarely interfered with the interpretation (figs. 1 *C* and 3 *A*). Six tracings, however, were distorted by this effect (fig. 3 *B*). This variability differed from that described above in that there was no appreciable change in amplitude and the form reflected the site on the base line the complexes fell, not the phase of respiration. If the breathing was quieted or held, clearly normal ballistocardiograms were obtained (fig. 3 *B* (2)).

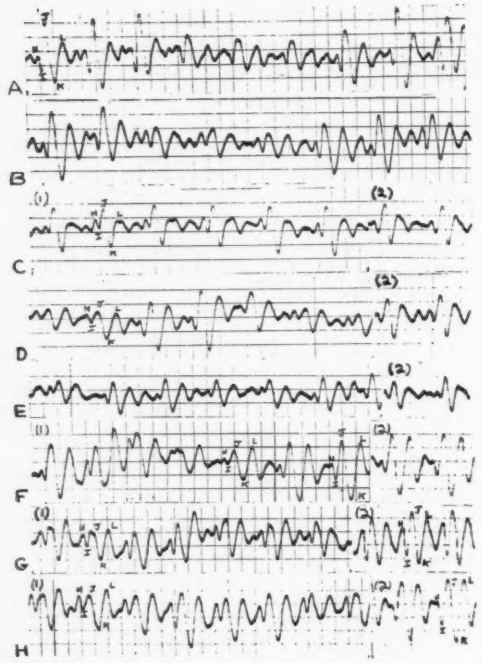

FIG. 2. Variations related to respiraton as described in the text. The short strips to the right are from the same subject with respiration held. These tracings are arranged approximately in order of increasing variation of the expiratory complexes from the basic pattern. Note the progressively disproportionate shortening of the I waves. The age, height, weight, and blood pressure of these subjects were as follows: *A*, 23, 66 inches, 140 pounds, 110/60; *B*, 24, 71 inches, 175 pounds, 120/74; *C*, 24, 67 inches, 140 pounds, 116/62; *D*, 23, 67 inches, 155 pounds, 110/68; *E*, 23, 66 inches, 140 pounds, 112/74; *F*, 24, 70 inches, 162 pounds, 120/76; *G*, 23, 68 inches, 155 pounds, 122/74; and *H*, 25, 68 inches, 150 pounds, 114/64.

4. A distortion similar to the high HIJ-deep K-prominent L pattern described above also appeared on most tracings which also showed a heart rate of 100 beats per minute or more (fig. 4 *A* and *B*). This effect did not disappear when the breath was held [fig. 4 *B* (2)], unless the rate also slowed [fig. 4 *A* (2)]. The degree of abnormalcy was considered grade 3 for five records, grade 2 for three records and grade 1 for six records. This effect is attributed to the superimposition of the HIJ deflections on after waves of the preceding complexes.[25] These records emphasize that tachycardia so distorts the ballistocardiogram that interpretation is precluded.

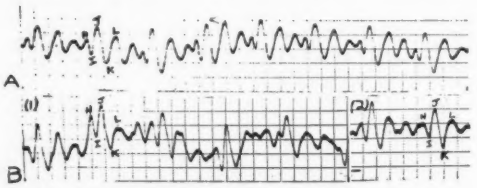

FIG. 3. Weaving of the base line due to respiratory motion. *A*, No distortion of the ballistocardiogram. *B* (1), Marked distortion. *B* (2), Same subject as *B* (1) with breath held, normal ballistocardiogram.

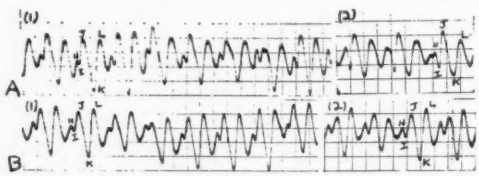

FIG. 4. Effects of tachycardia on the ballistocardiogram as described in the text. This distortion precludes interpretation.

5. The H waves varied from relatively tall [fig. 5 *A* (1)] to absent [fig. 5 *A* (2)]. On one record the H waves in a few expiratory complexes were as tall or taller than the J waves (fig. 5 *B*). This did not occur when the breath was held [fig. 5 *B* (2)]. On another tracing a few complexes with exceptionally large H waves were noted (fig. 5 *C*). These two tracings were classified as possible grade 1 abnormal records.

6. The I wave variations were considered in paragraph 2. The J and K waves were very stable. Minor notching of the J waves was

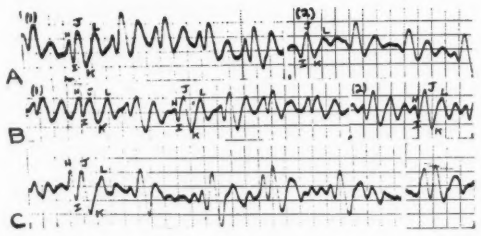

FIG. 5. Variations of the H waves: *A* (1), normal tall H waves. *A* (2), small or absent H waves. *B* (1), note the unusually tall H waves in the second and seventh complexes. *B* (2), same subject with respiration held: the tall H waves are not seen. *C*, note the very large H waves in the first, fourth and tenth (inserted) complexes. The age, height, weight and blood pressure of these individuals were: *A* (1), 23, 67 inches, 145 pounds, 110/64; *A* (2), 24, 69 inches, 210 pounds, 108/70; *B*, 24, 67 inches, 140 pounds, 120/74; and *C*, 24, 62 inches, 150 pounds, 116/70.

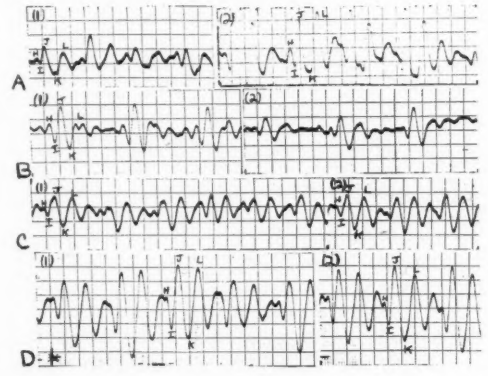

FIG. 6. Variations of the K and L waves. *A* (1), notched K waves. *A* (2), notched, shortened K waves in some complexes. *B* (1), normal "notched" L waves. *B* (2), normal rounded L waves. *C* (1), minor notching of some J waves and tall L waves. *C* (2), same subject with breath held. The notching of the J waves is less evident. *D* (1), tall L waves. *D* (2), same subject with breath held. The age, height, weight and blood pressure of these subjects were as follows: *A* (1), 23, 65 inches, 205 pounds, 124/80; *A* (2), 21, 69 inches, 155 pounds, 116/68; *B* (1), 25, 70 inches, 160 pounds, 110/62; *B* (2), 24, 72 inches, 195 pounds, 120/68; *C*, 25, 69 inches, 160 pounds, 114/70; *D*, 24, 72 inches, 180 pounds, 110/62.

noted on two records (fig. 6 *C*) but this practically disappeared when the breath was held [fig. 6 *C* (2)]. A persistent small single notch of most K waves was observed on two other tracings [fig. 6 *A* (1)]. On one record some of the K waves were shortened and notched [fig. 6 *A* (2)], but this disappeared when respiration was suspended. These five tracings are probably normal, but if strictly interpreted, the two with notched J waves would be grade 2 abnormal records, the two with notched K waves would also be graded 2 and the one with shortened K waves would be graded 1.

7. The L waves were quite inconstant, varying in size and angularity (figs. 1 *A* and *B*, 6 *B*). Nineteen tracings were normal except that the L waves were as tall or taller than the J waves (fig. 6 *C*, *D*). Since relatively tall L waves are a characteristic of records obtained with this type of ballistocardiograph,[34, 36] and since many of the L waves on the 273 clearly normal ballistocardiograms were only slightly less prominent, these records were considered normal.

8. The 22 subjects whose ballistocardiograms were considered abnormal did not differ at all from the group as a whole in age or in the height of the blood pressure. However, their average height was 67 inches as compared to 69 inches for the total group, and their average weight was 6 pounds less than the average of 167 pounds for the entire series. These differences were not statistically significant.

SUMMARY AND CONCLUSIONS

1. The basic characteristics and variability of the ballistocardiogram as obtained from a well screened young population on an equalized portable electromagnetic ballistocardiograph have been described.

2. The most frequently observed variation involved changes in the expiratory complexes which, when of sufficient degree, have been considered abnormal.[2, 6, 13, 17] Ten (3.2 per cent) records were classed grade 1 and five (1.6 per cent) were classed grade 2 abnormal tracings for this type of change.

3. Variations of the H, J and K waves add a possible three (1.0 per cent) grade 1 abnormal records and four (1.3 per cent) grade 2 abnormal records.

4. The distortion due to tachycardia was described, and it is clear that such ballisto-

cardiograms cannot be interpreted. These records were not included in these percentages.

5. Tall L waves were noted in 19 (6.2 per cent) of the records and were not considered abnormal.

6. This study confirms the authenticity of the widely described criteria of normal, but demonstrates that variability sufficient to invoke a classification of grade 1 or 2 abnormalcy may occur in a small (7.2) percentage of clearly normal subjects. When respiration was suspended, only three (1.0 per cent) of these ballistocardiograms remained questionably abnormal.

Acknowledgments

The authors wish to express their gratitude to Sergeant Thomas A. Stone, Corporal George W. Neher, Corporal Paul D. Grove and Mrs. Wanda McNulty for their aid in the preparation of this paper.

Sumario Español

Se registraron balistocardiogramas en 319 bien seleccionados soldados en un balistocardiógrafo electromagnético electricamente igualizado. Los trazados fueron analizados para los patrones básicos y para variaciones. El criterio convencional de lo normal se confirmó. La variación que se observó con mas frequencia consistió en los cambios de los complejos registrados durante expiración, que cuando de suficiente grado se asemejaban a las variaciones descritas como anormales. Ondas L prominentes se observaron comunmente. Variaciones en las ondas J y K fueron raras. Una anormalidad grado I o II se notó en 22 trazados, pero cuando se abolió la respiración, solamente tres persistieron discutiblemente anormales.

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Thiamine Deficiency in Organic Heart Disease

By MICHAEL G. WOHL, M.D., CHARLES R. SHUMAN, M.D., RICHARD TURNER, M.D., AND JOHN J. FITTIPOLDI, JR., M.D.

Since cocarboxylase, derived from thiamine, is necessary for normal utilization of pyruvate by heart muscle, the importance of adequate body stores of thiamine in patients with chronic heart disease is quite obvious. In order to investigate the occurrence of subclinical thiamine deficiency in patients with chronic heart disease, the thiamine was determined in the four-hour specimen of urine after loading dose in 35 male patients with congestive heart failure and compared with thiamine excretion in 17 persons free from cardiac disease. It was found that the noncardiac group had a significantly higher excretion of thiamine after a loading dose than patients with heart disease. Nine patients with severe heart failure receiving mercurial diuretics in the course of treatment were studied using 24-hour urine collections before, during and after the injection of the mercurial. The 24-hour urinary thiamine content was measured, demonstrating significant increases in thiamine excretion with mercurial diuresis.

THAT thiamine deficiency may be a primary cause of serious cardiac disturbances is well established.[1-5] However, it is not generally recognized that organic heart disease, per se, constitutes a conditioning factor in the development of thiamine deficiency. Such a possibility fits in quite well with the symptoms and signs accompanying chronic heart disease. These include anorexia associated with congestive failure or drugs used in its treatment, venous stasis of the gastrointestinal tract and hepatic congestion and dysfunction. All these are factors of cardinal importance in restricting the intake of food rich in thiamine and/or impairing absorption and utilization of thiamine. Another factor which may further deplete the already decreased stores of thiamine in the body is the conventional use of mercurial diuretics in patients with chronic heart disease. Since cocarboxylase derived from thiamine is essential for normal utilization of pyruvate by heart muscle, the clinical importance of inadequate thiamine stores is quite obvious. Therefore research was recently initiated on certain phases of thiamine metabolism in persons with chronic heart disease. This preliminary communication deals with the incidence of subclinical thiamine deficiency in patients hospitalized for treatment of cardiac failure. The effect of mercurials on thiamine excretion will be briefly summarized here. Details of this study will be reported elsewhere. Other phases of a larger study of this problem will be reported on from time to time.

For determination of subclinical thiamine deficiency, the method of Hochberg and Melnick[6] was chosen as the most convenient, and it compares favorably with the procedure used by Robinson, Melnick and Field.[7]

METHOD AND MATERIAL

The method for determination of thiamine in the urine is based on the reaction between the vitamin and diazotized aminoacetophenone as developed by Melnick and Field[8] and Melnick and Hochberg.[6]

The thiamine excretion was determined on a four hour urine specimen from persons who had had no food for 12 hours and who received 0.35 mg. of thiamine per square meter of body surface intramuscularly. In many of the patients the determination of thiamine was performed in duplicate. According to Hochberg and Melnick, when a person excretes in four hours less than 100 micrograms of thiamine after the load test, thiamine deficiency is present. The four hours urine method was employed for two reasons. First, some difficulties were encountered in getting accurate 24 hour urine collections on patients in a general medical ward, and second, it has been shown that when thiamine is administered parenterally most of the total amount excreted is found in the first four-hour urine sample.

Thirty-five male patients were selected from the medical wards of the Philadelphia General Hospital. The patients were hospitalized for treatment of cardiac failure. The causes leading to cardiac failure were hypertension, arteriosclerotic coronary artery

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disease, and rheumatic heart disease. Alcohol addicts and patients with disorders known to lead to avitaminosis were eliminated from the study.

The ingested daily diet of the patients contained on the average 0.9 mg. to 1 mg. thiamine and provided 1800 to 1900 calories. The calculations were based on tables compiled by Bowes and Church.[9] The patients were on such a diet for a period of 10 days prior to the thiamine clearance determination. An effort was made to have the patients under study consume the daily allowed food. However, in some instances a portion of the food was not eaten. We are fully aware that this factor may contribute to low levels of thiamine excretion. But the validity of the results of the over-all study is not impaired since our object is to evaluate the status of thiamine nutrition in cardiac patients as they are observed in a general hospital under the ordinary hospital care. The food intake of our patients represents probably the usual dietary experiences of hospitalized cardiac patients. Supplementary vitamins were discontinued for six days prior to and during the study. Digitalis was continued; mercurial diuretics, however, were omitted for six days prior to and during the study.

Controls. Seventeen persons free from cardiac disease served as controls. Thirteen were hospitalized patients of similar age and sex distribution as the cardiac group; they were served the same food as the cardiac patients and did not receive supplemental vitamins; four subjects in the control group were interns; their diet was more liberal and contained on the average 1.2 mg. of thiamine and 2000 to 2200 calories.

The Effect of Mercurials on Thiamine Excretion

The effect of mercurial diuresis upon thiamine excretion was investigated in a group of nine patients with chronic congestive heart failure. Each of these had been under treatment with digitalis, mercurials, and salt restricted diets for periods ranging from six months to four years; most of these patients had been given supplemental vitamins during the treatment period. Included in the group were five patients with hypertensive heart disease, three with arteriosclerotic heart disease, and one with mitral stenosis. Prior to the collection of urine, vitamin supplements and mercurials were stopped and the majority of patients were maintained on an 1800 caloric diet providing approximately 1.0 mg. of thiamine daily. After several days on this preparatory regimen and prior to mercurial injections the 24 hour urine collections were made as control for the urine collections obtained on the day of the mercurial and the day immediately following the mercurial (Thiomerin or Mercuhydrin, 2 cc. intramuscularly). The daily urine samples were measured, a 200 cc. aliquot was acidified and kept refrigerated until the thiamine determinations were made by the method described.

The data were analyzed to determine whether any relationship existed between the volume of urine and the urinary thiamine content, the volume of urine excreted on control days and the days of mercurial injection as well as the day following the mercurial. The principal interest of this phase of the study centered about the comparison of the thiamine excretion in absolute terms as well as in micrograms per cubic centimeter between the control and mercurial periods. The results are reported in table 3.

Results

Table 1 and figure 1 present results of the four-hour thiamine clearance in both cardiac patients and control subjects. The mean for the 35 cardiac patients was 40.6 micrograms with a standard deviation of 24.9 micrograms; the mean for the 17 control subjects was 139.5 micrograms with a standard deviation of 73.5 micrograms. The difference between the means was tested by means of the t test, which showed a probability of less than 0.001. Hence it may be concluded that noncardiac subjects have a significantly higher mean excretion of thiamine than cardiac cases. The difference between variances was tested by means of the F test, which showed a probability of less than 0.001. If all subjects are kept, this would mean

Table 1.—*Results of the Four-Hour Thiamine Clearance Test in 35 Male Cardiac Patients and 15 Control Male Noncardiac Patients*

Microgram/4 Hrs.	Number of Cases	Percentage of Cases
Male Cardiac Patients		
5–24	9	25.7
25–44	15	42.9
45–64	3	8.6
65–84	6	17.1
85–104	2	5.7
Total	35	100.0%
Control Male Noncardiac Patients		
70–89	4	26.6
90–109	3	20.0
110–129	3	20.0
130–149	3	20.0
150–169	1	6.7
170–189	1	6.7
Total	15	100.0%

that noncardiacs are significantly more variable than cardiac cases (table 2).

It was noted, however, that two noncardiac subjects were "unusual" in that they contributed an excessive proportion of the total variance. When these two subjects (with values of 250.8 and 379.3 micrograms) were eliminated, the mean for the 15 remaining noncardiac subjects was reduced to 116.1 micrograms and the standard deviation to 30.4 micrograms. This mean was still significantly higher than the mean for cardiac patients (probability of t less than 0.001), but the variance for the noncardiac group did not differ significantly from that of the cardiac group (probability of F greater than 0.05). From table 1 and figure 1 it becomes apparent that the lowest thiamine excretion of the 68.6 per cent of the cardiac patients ranged in four hours from 4.5 to 44.5 micrograms, while the lowest values of the 66.6 per cent of the control noncardiac patients ranged from 69.5 micrograms to 129.5 micrograms of thiamine.

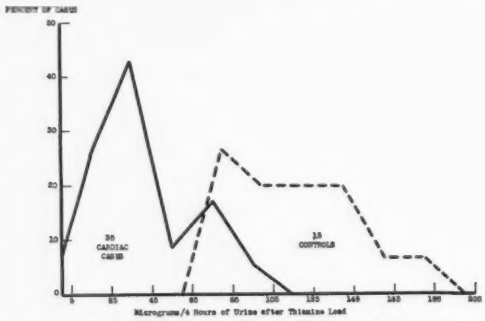

FIG. 1. Results of a four-hour thiamine clearance test in 35 male cardiac cases and 15 male controls.

TABLE 2.—*Summary of Results of Four-Hour Thiamine Clearance Test Mean, Standard Deviation, Highest Value, Lowest Value for 17 Male Controls and 35 Male Cardiac Patients*

	Microgram in Urine 4 Hours After Thiamine Load		
	Control		Cardiac
Number of Cases	17	15*	35
Mean	139.5	116.1	40.6
Standard Deviation	73.5	30.4	24.9
Highest Value	379.3	180.6	101.9
Lowest Value	72.9	72.9	6.0

* Two of the 17 controls had such a high value that they "distorted" both the mean and the standard deviation. The analysis was carried out, therefore, both including and excluding these two.

In 12 other cardiac patients and seven control subjects both the fasting thiamine excretion and the four-hour urinary excretion after the test dose of thiamine were determined. The fasting urinary thiamine in the cardiac patients varied between 7 micrograms and 57.6 micrograms. The higher excretion levels were in the females. In the control cases the fasting thiamine excretion varied between 53.5 micrograms and 119.9 micrograms.

It is not definitely known whether the amount of urinary thiamine excreted after an intramuscular load test, or, for that matter, the blood thiamine level is a valid measure of tissue storage of the vitamin. However, the extremely low urinary levels in our cardiac patients tend to indicate that the nutritional status of the patients with respect to thiamine was subnormal. There is cogent evidence to suggest that a marked subnormal thiamine status is associated with thiamine tissue depletion.[8, 10] It is to be noted that there were marked individual differences in the urinary thiamine excretion. However, the four-hour thiamine excretion in the same individual tended to remain on the same low level from day to day while the four-hour urinary excretion in the control group varied considerably among individual patients and in the same individual from day to day. The number of cases in which fasting urinary thiamine excretion was determined is too small to permit any conclusions. A larger number of determinations may prove it to be a good routine laboratory screening test. This agrees with the conclusions of Lowry.[11] Daily fluctuations of thiamine excretion are much smaller when thiamine intake is low than when thiamine intake is high. The chances of misdiagnosing thiamine deficiency on a one-day excretion are therefore also less.[12]

Effect of Mercurials on Thiamine Excretion

The results of the thiamine excretion studies as affected by mercurial treatment were of

considerable interest. It was initially determined that among individuals there was no evidence that a high volume of urine was associated with an elevated absolute amount of thiamine in the urine. It is to be noted that on the day of mercurial administration and the following day the mean volume of urine was 1374 cc. and 1557 cc., respectively; the mean volume of the urine on the control day was 847 cc. Thus it is apparent that the mean volume of urine during mercurial administration was significantly greater than on the control day (the probability of t equals less than 0.01 and 0.02, respectively).

in those periods wherein urine volumes were greatest. This gives added significance to the thiamine losses observed during and immediately after the mercurial administration. The data demonstrate that marked urinary excretion of the water soluble vitamin occurred as a result of the mercurial diuresis.

Discussion

There are several references in the literature to the occurrence of thiamine deficiency in hospital patients in England and in this country. However, records of studies on thiamine deficiency in cardiac patients are limited and

Table 3.—*The Mean Urinary Thiamine Excretion and Urine Volumes for Nine Patients During Control Periods and Following Administration of Mercurial Diuretics*

Patients	Control Day			Day of Mercurial			Day Following Mercurial		
	Thiamine content μg.	Volume of urine cc.	Thiamine volume μg./cc.	Thiamine content μg.	Volume of urine cc.	Thiamine volume μg./cc.	Thiamine content μg.	Volume of urine cc.	Thiamine volume μg./cc.
C. M.	280.7	500	.561	759.4	1120	.678	208.1	720	.289
E. R.	86.9	1260	.069	282.1	1800	.157	84.6	1800	.047
S. G.	54.1	1095	.049	293.8	1555	.189	517.1	1190	.435
F. B.	247.4	370	.669	366.5	740	.495	903.3	2700	.335
M. M.	156.4	1290	.121	574.8	990	.581	764.4	1250	.612
S. S.	91.1	858	.106	375.8	1467	.256	344.6	1220	.282
V. M.	61.0	700	.087	103.5	1000	.104	185.8	1250	.149
J. M.	24.3	450	.054	543.2	1400	.388	130.0	1450	.090
L. M.	211.8	1102	.192	329.3	2290	.144	636.6	2430	.262
Mean of all subjects.....	134.9	847	.212	403.2	1374	.332	419.4	1557	.278

As to the effect of mercurial therapy on thiamine excretion, the results recorded in table 3 indicate that on the day of mercurial administration the mean value of thiamine excretion was 403.2 micrograms per 24 hours and the following day 419 micrograms per 24 hours as compared with the mean value of 134.9 micrograms per 24 hours for the control days. The probability of t for these values was 0.01. However, the mean concentration of thiamine per cubic centimeter of urine was not significantly different when mercurials were administered as compared with control values.

The difficulties encountered in collecting 24-hour urine specimens necessary for this study are appreciated. However, if collection errors were randomly distributed throughout the groups, the largest losses should have occurred

do not provide a basis for statistical treatment. Goodhart and Sinclair,[14] using the amount of the cocarboxylase determined in the blood as a method for estimating thiamine deficiency, found significantly low values in 6 out of 13 subjects with cardiac failure. One diabetic patient with congestive heart failure had a low value (1.0 microgram) of cocarboxylase which increased considerably (5.5 micrograms) after therapy with vitamin B_1.

In this country Robinson and co-workers[7] found excretion of thiamine less than 7 per cent of an oral 5 mg. test dose in six out of seven patients with cardiac decompensation. These low excretion values were interpreted as indicating thiamine depletion. Goldsmith,[15] using the lactate-pyruvate ratio as a method of determining thiamine deficiency, found low

lactate-pyruvate ratios in four out of nine patients with heart disease and considered this to be indicative of thiamine deficiency. The reports of these investigators and our findings suggest that thiamine deficiency in association with cardiac disease is more than a coincidence.

The question arises as to the factors responsible for the thiamine deficiency in patients with chronic heart disease. Doubtless there are many reasons for it. It is quite likely that the anorexia and low thiamine intake in the diet play an important role.

Another factor involved in disturbed thiamine metabolism is the anoxia associated with heart disease. Anoxia of the intestinal tract because of passive congestion may interfere with absorption of the small amount of thiamine supplied by the inadequate food intake. A further cause of thiamine depletion in chronic cardiac disease is probably the conventional use of mercurial diuretics. Although mercurial diuretics are most effective in controlling edema of congestive heart failure, their effect upon excretion of thiamine has not been generally appreciated. Williams and Bissel[13] observed marked urinary loss of thiamine following injection of Mercuphyline in two patients with congestive heart failure. Our results tend to demonstrate that the levels of thiamine excretion following administration of mercurials are significantly increased over the levels observed on the control days. Because the over-all analysis does not reveal a direct correlation between urine volume and urinary thiamine concentrations, we are led to suspect that the loss of thiamine occurs as a result of the influence of the mercurial diuretics upon the renal tubular mechanism for thiamine reabsorption. The lack of a satisfactory method for measurement of blood thiamine renders the study of renal mechanism for thiamine excretion difficult.

The patients considered in these studies did not manifest clinical signs of thiamine deficiency. The probable explanation for the absence of clinical findings of vitamine B_1 deficiency is the fact that in patients of the type used in this study the caloric intake is generally reduced to a level at which subnormal thiamine supplies may be adequate for non-appearance of gross clinical manifestations. Furthermore, there is a possibility that thiamine deficiency may occur in the cardiac muscle, since it is peculiarly sensitive to deprivation of thiamine,[16] whereas other organs may be free of that deficiency. Investigation of this problem is indicated.

Summary

Thirty-five patients under treatment for chronic heart failure were given loading doses of thiamine, using 0.35 mg. per square meter of surface area, following which the four-hour urinary thiamine content was measured by the method of Hochberg and Melnick. Seventeen control subjects selected from patients with noncardiac disease whose nutritional status was good or from the hospital personnel were studied by the same method. The mean thiamine excretion of the group with congestive heart failure was 40.6 micrograms with a standard deviation of 24.9 micrograms. The mean excretion of the control group was 139.5 micrograms with a standard deviation of 73.5 micrograms. Statistical analysis of the data indicated that the noncardiac group had a significantly higher excretion of thiamine after a loading dose than the patients with heart disease.

Nine patients with severe heart failure who were receiving mercurial diuretics in the course of treatment were studied, using 24-hour urine collections before, during and after the injection of the diuretic. The 24-hour urinary thiamine content showed significant increases in thiamine excretion with mercurial diuresis.

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Sumario Español

Como la cocarboxilasa derivada de la tiamina es necesaria para la utilización normal del piruvato por el miocardio, la importancia de las reservas de tiamina del cuerpo en pacientes

con enfermedad crónica cardíaca es muy obvia. Para poder investigar la incidencia de deficiencias subclínicas de tiamina en pacientes con enfermedad cardíaca crónica, el nivel de tiamina se determinó en especimenes de orina a las cuatro horas de habersele dado a 35 pacientes varones con decompensación cardíaca una dosis de carga y comparando la excreción de tiamina con la de 17 personas libres de enfermedad cardíaca. Se encontró que el grupo no cardíaco tuvo una excreción de tiamina significativamente mas alta luego de la dosis de carga que los pacientes con enfermedad cardíaca. Nueve pacientes con decompensación cardíaca severa recibiendo diuréticos mercuriales durante el curso del tratamiento, fueron estudiados usando la colección de orinas por 24 horas antes, después y luego de la inyección del mercurial. El contenido de tiamina en el especimen de orina de 24 horas se determinó, demostrándose un aumento significativo en la excreción de tiamina con la diuresis mercurial.

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Pattern of Failure of the Homografted Canine Heart

By SIGMUND A. WESOLOWSKI, M.D., AND JOHN F. FENNESSEY, M.D.

A series of puppy hearts was homografted into the necks of adult dogs. The grafts were followed for viability by palpation and by electrocardiograms. Of the grafts studied none functioned longer than one week. Others removed on successive days after transplantation revealed a pattern of failure that suggests that incompatibility to the homografted canine heart is blood-borne.

THIS COMMUNICATION presents the pathologic pattern observed in a series of experiments during which the heart of a puppy was homografted into the neck of an adult dog after the method of Mann, Priestley, Markowitz and Yater.[1] This method of homotransplantation may be termed a "viviperfusion"; that is, vascular anastomoses are performed between the recipient neck vessels and the puppy heart vessels so as to perfuse the coronary circuit of the puppy heart in vivo. The only work load demanded of the transplant is the pumping of its own coronary circuit return by the right heart. Such a preparation may be convenient for the purpose of studying homograft incompatibility because viability of the graft at any time is easily determined by electrocardiographic means, thereby avoiding the necessity of repeated biopsy.

METHOD

The technic of transplant used is essentially that described in detail by Markowitz.[6] Eleven adult mongrel dogs weighing 27 to 60 pounds were used as the recipients. Healthy mongrel puppies weighing from 2 to 5½ pounds served as heart donors. The distal cut end of the recipient carotid artery was anastomosed to the central end of puppy heart aorta while the puppy heart pulmonary artery was anastomosed to the proximal cut end of the recipient external jugular vein. The anastomoses were made using continuous everting mattress sutures of 6-0 arterial silk. (See fig. 1.)

Three grafts were followed until they were no longer viable. These three grafts were completely necrotic on the seventh postoperative day. The five succeeding grafts were interrupted on consecutive days after grafting; that is, the grafts were removed in toto on the second, third, fourth, fifth and sixth days respectively after transplantation. All of these interrupted specimens were viable as evidenced by the presence of electrical activity and a visible beat at the time of removal. These specimens were preserved in 10 per cent formalin and examined histologically. In the ninth experiment the graft was enclosed in a plastic bag and interrupted on the fourth day as a viable graft to ascertain whether the exclusion of local factors was related to the degree of graft necrosis. In one experiment daily aspiration of serous fluid was necessary to decompress the graft. In one experiment incision and drainage of a neck abscess was done on the fourth postoperative day. Two other grafts were excluded from this series on the basis of thrombosis of the carotid-aortic anastomosis.

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OBSERVATIONS

Clinical Observations

When the graft was first inserted there was initial ventricular fibrillation which spontaneously reverted within a matter of minutes to a normal sinus rhythm at a rate varying between 140 and 200 beats per minute. With one exception the grafts remained within this rate range until interruption. In one graft the rate rose from 185 to 300 on the fourth postoperative day and remained at this rate until interruption on the fifth day after operation. The viability of the grafts could be easily followed by direct palpation of a beat through the skin of the recipient's neck. Viability was checked by electrocardiography. At the time of interruption of the grafts a typical picture was encountered. The epicardium of the graft was surrounded by loose fibrin deposit. The sur-

rounding recipient tissues were swollen and edematous. Graft necrosis became more marked as the age of the graft increased. The six day graft, which still pulsated visibly and possessed electrical activity, showed necrosis of more than 50 per cent of the total myocardium.

Electrocardiographic Observations

Electrocardiographic tracings were recorded from the recipient animal before and directly after the grafting procedure, and daily thereafter until interruption of the graft. The following leads were routinely recorded: the three standard limb leads and V leads with the exploring electrode located serially in the suprasternal notch, on the right neck and on the left neck over the transplant. The electrical activity of the transplant is fairly well localized to the left neck of the recipient. The V-lead tracing over the right neck or suprasternal notch shows only or mainly complexes originating from the recipient's heart, thereby facilitating identification of the two independent cardiac cycles recorded over the transplant. That two independent cardiac cycles are recorded is shown by the following: (1) there are many more QRS complexes appearing in the left neck tracing than in the right neck tracing; (2) there are two types of QRS complexes occurring at two different and regular rates; (3) the two types of QRS complexes occur in one another's absolute refractory periods; and (4) the complexes add algebraically when occurring simultaneously. (See fig. 2.) If the anterior surface of the puppy heart is superficial the electrocardiographic complexes are upright (fig. 3); if the posterior surface of the heart is superficial the complexes are inverted (fig. 2).

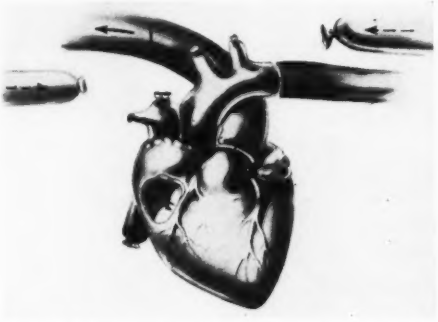

FIG. 1. Drawing illustrating the technic of viviperfusion of the puppy heart. (1) Proximal end of transected recipient left external jugular vein anastomosed to the puppy heart main pulmonary artery to receive the output of the right ventricle. (2) Distal end of transected recipient left common carotid artery anastomosed to puppy heart aorta for supply of the puppy heart coronary circulation. Solid arrows depict the blood flow during viviperfusion; the dotted arrows show the direction of the interrupted blood flows in the left external jugular vein and common carotid artery.

On the first day of the graft the voltage amplitude of the graft QRS complex is comparable to a normal canine limb lead II. As the graft age increases the voltage markedly diminishes, probably because of the accumulation of edema fluid and fibrin around the graft. At the time of interruption of the graft, when the incision is opened and the fibrin is cleared away, the QRS amplitude is restored. In the single experiment where the graft was encased in a plastic sleeve, it was noted that the plastic prevented the propagation of the graft electrical activity to the overlying skin. However, complexes of good amplitude could be obtained by inserting the exploring electrode through the drain with no diminution of QRS amplitude during the four days that the graft was allowed to function.

Pathologic Observations

Gross Pathology. The two- and three-day hearts showed very little except a thick fibrin deposit on the epicardial surface and rare petechial bleeding into the endocardium. They were well contracted and free of thrombosis. The four-, five- and six-day hearts showed much more marked changes. Foci of softening and bleeding were grossly visible in the ventricular musculature. The right heart assumed a dilated character. Thrombi appeared in the atria. The six-day heart showed practically complete degeneration of the ventricular and atrial myocardium which was yellowish tan in color and had a tendency to fragment into lamellae. The vascular anastomoses were free of microscopic thrombi, except for the two excluded

grafts already mentioned; both of these hearts weighed less than 20 Gm.

Microscopic Pathology. The earliest change observed is in the one- and two-day hearts which show marked cellular infiltration beneath the endocardium. The reacting cells are chiefly histiocytes with an occasional eosinophil. This infiltrate has a tendency to extend into the underlying myocardium along the larger thebesian channels. The myocardium at this time shows a variable degree of serous edema without appreciable cellular reaction. There is fibrin deposition upon, and round cell infiltration into, the epicardium. On the third day small patchy areas of myocardial necrosis are seen in the midportion of the myocardium. There is now a diffuse, cellular infiltration of the myocardium and more marked intercellular edema. The infiltrate is most marked about large and small vessels. On the fourth, fifth and sixth days the changes are largely quantitative. The patchy areas of necrosis become larger, more numerous, confluent and eventually involve large areas of the myocardium. The myocardial fibers show successively swelling, fatty vacuolization, de-

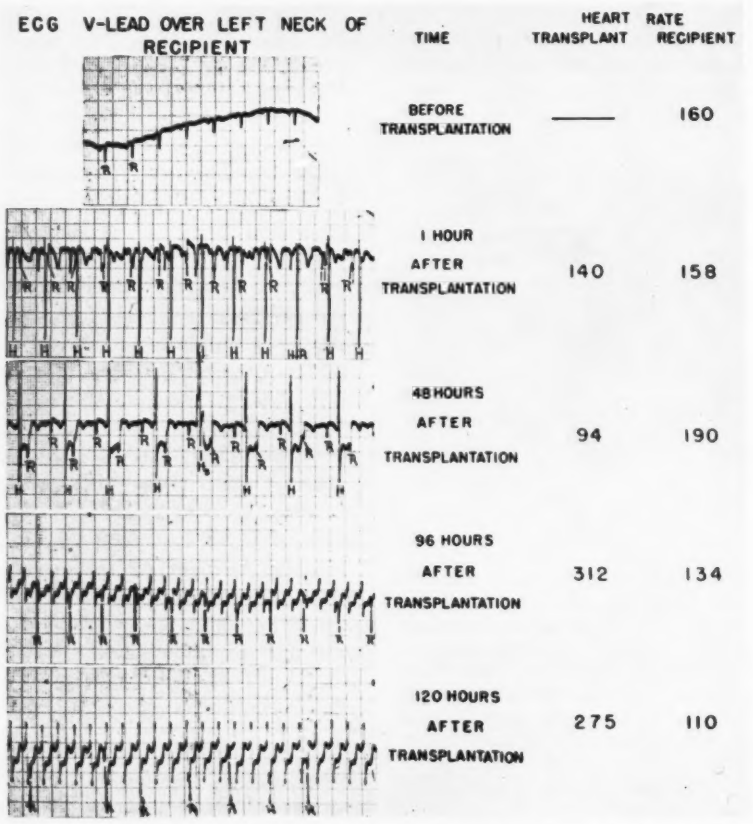

FIG. 2. Electrocardiographic tracings recorded over the site of the homografted heart. In the various tracings the major deflection of the electrocardiographic complexes originating from the recipient heart are marked with R, while the major deflections originating from the homograft are marked H. In the two lower tracings the dominant pattern of ventricular tachycardia originates from the homograft. The posterior surface of this graft was superficial resulting in inversion of the graft electrocardiographic complexes.

crease in prominence of and loss of cross striations, loss of sarcoplasm with collapse of the sarcolemmal sheath. There is a marked cellular reaction to the necrotic fibers with many polymorphonuclear leukocytes phagocytizing debris, and ectasia and dilatation of capillaries with intense congestion and petechial hemorrhage. At six days an estimated one-third of the ventricular myocardium is microscopically viable. Within the atria, which show changes at least as severe as the ventricles, mural thrombosis sets in on the damaged endocardium. Typical microscopic changes in a four day graft are illustrated in figure 4.

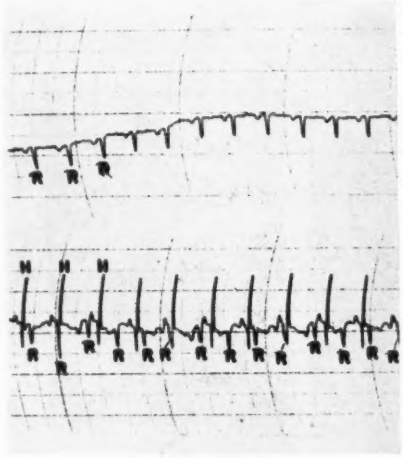

FIG. 3. Electrocardiographic tracings recorded over the site of a homografted heart with the anterior surface of the heart superficial. Note the upright electrocardiographic complexes originating from the grafted heart. *Upper tracing:* before transplantation. *Below:* after transplantation.

The pattern of myocardial necrosis is progressive in the chronologically interrupted hearts. This progression can be summarized as follows:

One- to two-day grafts: Serous edema separating the fibers but with the fibers still well preserved; cellular infiltration mostly confined to the endocardium and the perivascular area about larger blood vessels.

Three-day graft: More marked cellular infiltration involving much of the myocardium but still radiating out from vascular channels; more edema richer in protein; small areas of necrobiosis of centrally located muscle fibers.

Four- to six-day grafts: Marked cellular infiltration most severe about epicardium and endocardium but also diffusely present in atrial and ventricular myocardium; increase in number and size of areas of infarction, confluence of areas of infarction; widespread degeneration and necrobiosis of muscle fibers. The presence of the plastic sleeve did not change the four-day histologic picture.

Seven- to ten-day grafts: Complete degeneration with necrosis and liquefaction.

DISCUSSION

In correlating these observations with those of Medawar,[2-5] it would appear that a homografted canine heart exhibits an initial "take" period of up to six days as evidenced by a palpable beat and the presence of electrical activity. Beginning on the third day there is microscopic evidence of necrosis in the graft. That this necrosis is on the basis of homologous tissue incompatibility seems likely. There is the possibility that the heart graft failure may be a late manifestation of the period of 45 to 90 minutes anoxia that the heart is subjected to while the anastomoses are being made. However, Marcus, Wong and Luisada[7] observed failure of homografted hearts in spite of a continuous perfusion of the heart by means of a third dog while anastomoses were being performed. These hearts were beating constantly without any period of anoxia during the entire transplantation procedure and yet failed following an initial "take" period.

There are two possible sites of incompatibility; that is, incompatibility of host to the donor vascular network with resultant vascular occlusion and myocardial infarction, or an incompatibility acting directly upon the myocardium. If the necrosis observed in this series of grafts were on the basis of ischemic myocardial infarction, then the earliest involved areas should be the areas of poorest blood supply, namely the subendocardial myocardium. But the first areas of necrosis seen were small patches of degeneration in the midportion of the ventricular myocardium.

There was observed no gross or microscopic arterial lesions to account for the necrosis.

The central location of the patchy myocardial necrosis is evidence against the operation of a localized or generalized cellular response; the fact that the necrosis followed the same pattern when the graft was isolated by means of a plastic sleeve fairly well rules out this possibility. These findings, therefore, suggest that the necrosis of the homografted canine heart is primarily caused by humoral factors acting directly upon the myocardium.

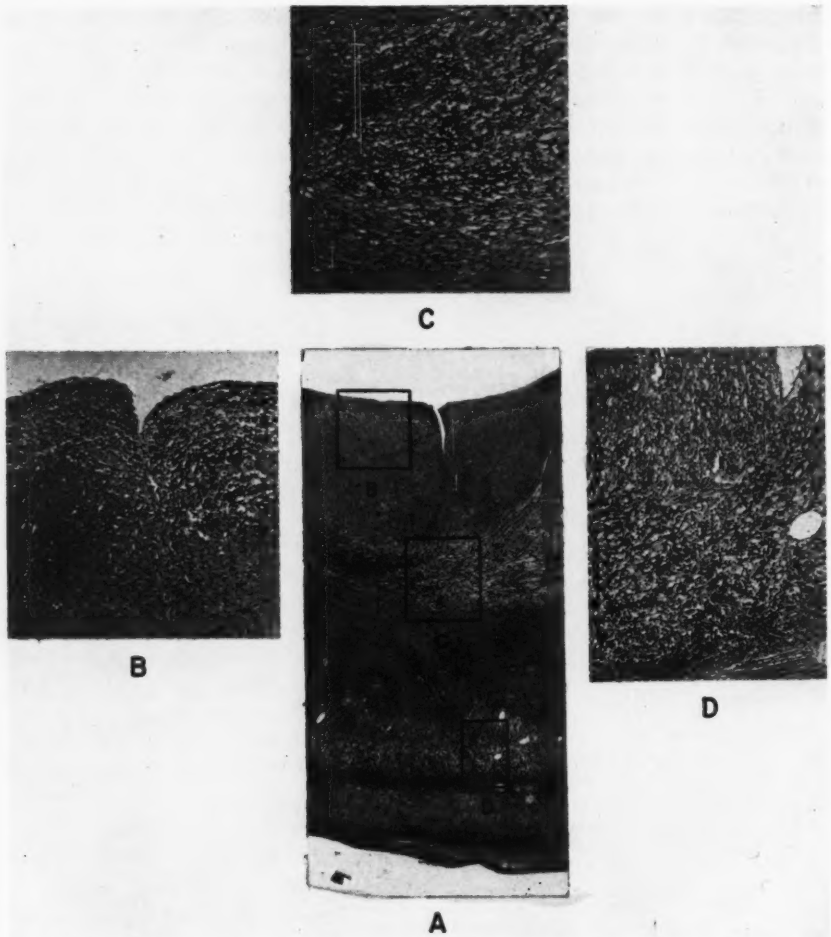

FIG. 4. Photomicrographs of right ventricular wall of four-day interrupted homograft showing typical microscopic changes. *A* is a low power view and *B*, *C*, and *D* are high power views. *A* shows the entire thickness of the right ventricular wall with characteristic central necrobiosis of the myocardium, thickened endocardium and epicardium and fibrin deposit on the surface of the epicardium. *B* illustrates the character of the endocardial infiltration. *C* demonstrates the central myocardial necrobiosis. *D* shows the diffuse epicardial infiltration.

SUMMARY

1. The feasibility of experimental homotransplantation of the canine heart as described by Mann, Priestley, Markowitz and Yater has been confirmed.

2. Of 11 transplants attempted, nine were

technically successful. The two failures are attributed to thrombosis at the arterial anastomosis. The successful transplants beat for at least 48 hours; those that were not interrupted beat for four to six days. All eventually failed after an initial "take" period. Viability was confirmed by electrocardiography.

3. From study of grafts removed at various times after implantation, a definite pattern of graft failure was observed.

Sumario Español

Una serie de corazones de cachorro fueron homoinjertos en los cuellos de perros adultos. Los injertos fueron estudiados para viabilidad por medio de palpación y electrocardiogramas. De los injertos estudiados ninguno funcionó por más de una semana. Otros removidos en días sucesivos a la transplantación reveraron un patrón de fracaso que sugirió la incompatibilidad al homoinjerto canino ser de origen sanguíneo.

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CLINICAL PROGRESS

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Treatment of Cardiac Arrhythmias

By DAVID SCHERF

SIMPLE and fairly satisfactory rules have been established for the treatment of cardiac arrhythmias, but many problems remain unsolved. The latter chiefly concern those arrhythmias which are refractory to the generally accepted therapeutic measures. Patients still die from cardiac arrhythmias. Since readers of this journal are well acquainted with the routine aspects of the subject, emphasis in this discussion will be placed on the controversial points.

DISTURBANCES OF IMPULSE FORMATION

General Discussion

Two forms of disturbances of impulse formation are differentiated. Automatic impulses originating in an ectopic center may interfere with those formed by the normal pacemaker as in parasystole, dissociation with interference or competition between several auricular centers (shifting pacemaker). These disturbances require no therapy. A second and more common form is caused by abnormal stimulus formation as exemplified by extrasystoles, paroxysmal tachycardias, auricular flutter and fibrillation. Although little is known about the finer mechanism of these arrhythmias, one may assume that the membrane of the myocardial fiber in the "ectopic focus" is altered so that it does not become depolarized only once when a stimulus spreads over the heart; it is prone to develop electrical oscillations.[31] If the latter are large enough they induce a propagated impulse. These oscillations are set up by a beat of the basic rhythm (initiating beat). This accounts for the fact that an extrasystole and the first beat of a paroxysm of tachycardia, flutter and fibrillation are coupled to the preceding beat. Fibrillation differs from the other arrhythmias in that it appears to represent a situation in which many centers often are active.[29] Only rarely do ectopic abnormal impulses arise spontaneously, that is, independent of the last preceding beat of the basic rhythm.

This concept makes it easier to understand why arrhythmias can be influenced by a great variety of agents. Whatever influences the enzyme systems, the ionic environment and the membrane structure and function may abolish or create these arrhythmias. Extrasystoles or ectopic tachycardias may be arrested by such different ions or compounds as potassium or calcium, or by atropine and acetylcholine, neostigmine and banthine, epinephrine or ergotamine. This makes it also more comprehensible why the same substances (digitalis, quinidine, fagarine, potassium, epinephrine, calcium, acetylcholine and procaine) which abolish extrasystoles may also initiate them.

The therapy of this group of arrhythmias centers around quinidine, digitalis, vagotonic agents and procaine amide. Potassium, calcium, fagarine, magnesium, and procaine hydrochloride have less importance but will also be discussed. These measures either suppress the tachysystolic center, whereupon the sinus node resumes its role as pacemaker, or they slow the ventricular rate. The deleterious hemodynamic action of an arrhythmia is proportional to the ventricular rate.

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Quinidine remains the chief drug for suppressing ectopic arrhythmias. Recent investigations have correlated the blood concentration with the dosage and with the clinical effect.[12, 17, 34] The therapeutic effect and the blood level reach a maximum two hours after an oral dose. Significant was the finding that cumulation is definite though limited. When the drug is administered every two hours the peak concentration is attained after the fifth dose. Thereafter, the intake of the drug equals its disposal by the body. With intervals of four to six hours between doses the cumulative effect may be observed for several days so that the peak concentration may appear after two to four days. If increased blood levels are desired after the time limits just mentioned, it is necessary to increase either the size of the individual dose or the frequency with which it is administered.

A blood concentration of 6 to 8 mg. per liter is effective in successfully converting a majority of cases of auricular flutter or fibrillation into sinus rhythm. Data for ventricular arrhythmias are not available but clinical experience shows that in most instances a satisfactory response is obtained to small doses of quinidine. The doses at intervals of two hours are given five times, during daytime only. If quinidine is given every four hours the administration is best continued also through the night around the clock. The individual doses vary between 0.2 and 0.6 Gm. and depend on the weight of the patient. If the smaller dose is ineffective it is increased. It is of interest, that even the administration of large individual doses three times daily was no less effective than the small doses given more often.[22] These new results are thus in full agreement with the clinical experience gained many years ago. Considerable variations from the above cited averages may occur.

Blood levels of over 10 mg. per liter are occasionally necessary to convert an arrhythmia, but the incidence of toxic effects is very high. Determination of the blood level may sometimes aid in the management of a patient. If a relative large dose of quinidine is ineffective and there are no signs of toxicity, knowledge of the blood level may be helpful. If it is low, poor absorption may be assumed and the dose may be safely increased.

Quinidine often widens the QRS complex by decreasing the velocity of myocardial conduction. If the duration of the QRS complex becomes 0.11 second or more, caution is in order and it is best to stop the drug. If such patients and those with A-V block receive quinidine, sudden death from ventricular fibrillation has been observed repeatedly. Usually this is explained by the development of a circus movement, which is said to be facilitated by the appearance of block areas. However, increased excitability and formation of local potentials and oscillations distal from a block area have been observed in the nerve (Wedensky facilitation). It is probable that the response of the heart muscle fiber is similar.[31]

Administration of quinidine should also be interrupted when extrasystoles appear during therapy; usually they are of ventricular origin.

Effective therapy with quinidine is often prevented by the well known signs of hypersensitivity. Of these, diarrhea is most common and relatively harmless.

Often the vagolytic action[13] of quinidine, which appears after administration of normal therapeutic doses, is not fully appreciated. It abolishes the effect of carotid pressure. The sympathicolytic effect is also of clinical importance. Accordingly, vasodilatation is a common and often beneficial consequence of quinidine therapy.

The action of quinidine in these arrhythmias, which is so often incorrectly attributed to changes of the refractory phase, is due chiefly to an alteration of the center suppressing the firing of abnormal stimuli; there is also a diminution of the excitability of the myocardium. Actually certain drugs such as rawolfia abolish auricular fibrillation without exhibiting any influence on the duration of the refractory phase.[36]

Because of the occasional scarcity of quinidine, it is worthwhile to emphasize that quinine, although somewhat weaker than quinidine, is also effective in the treatment of ectopic arrhythmias.

Digitalis has a direct suppressive action on ectopic centers and readily abolishes extra-

systoles and tachycardias. It may rarely convert flutter or fibrillation to sinus rhythm. Its ability to prolong A-V conduction is valuable in controlling harmful effects of rapid ventricular activity in auricular tachycardias. On the other hand, digitalis is notorious for its propensity for provoking ventricular extrasystoles, ventricular tachycardia and, ultimately, ventricular fibrillation. Although it very rarely causes auricular extrasystoles, it does induce, on occasion, auricular tachycardias and even auricular fibrillation.

Before the physician employs digitalis for the treatment of an arrhythmia, he must be sure that this drug did not cause the arrhythmia. Ventricular extrasystoles and tachycardias caused by digitalis are characterized by a continuous change of form of the ventricular complexes, while the auricular tachycardias show A-V block. An arrhythmia caused by digitalis may persist for several weeks after the drug is stopped.

The manner in which digitalis is used in the individual arrhythmias depends on the type of the arrhythmia (see below).

Cocaine derivatives depress the excitability of the heart. Instillation of procaine or other derivatives into the pericardium diminishes ectopic beats during cardiac surgery. Since many substances are absorbed from the pericardium with the greatest speed, the effect is no better nor more prolonged than that of intravenous injection of the same drug. The local inhibitory effect of direct pericardial instillation may be detrimental. Novocaine applied to the sinus node of the dog abolishes immediately the activity of the node.[24] Intravenous injections of procaine hydrochloride have been proposed for the treatment of cardiac arrhythmias which appear during anesthesia with cyclopropane. Its usefulness under such circumstances and in clinical arrhythmias is very limited because of the brevity of its action. Within five minutes hydrolysis occurs in the blood stream. Procaine amide is more stable and therefore also more active after oral administration.[14] Clinically and experimentally, procaine amide has been found to be about one-fourth to one-third by weight as strong as quinidine. Therefore, one may substitute one for the other according to the rule that 0.25 Gm. (one capsule) of procaine amide is equivalent to 0.065 Gm. (one grain) of quinidine.[26]

For practical purposes, the action of procaine amide on the heart is identical with that of quinidine. It suppresses tachysystolic or extrasystolic centers, depresses myocardial conduction, prolongs the Q-T interval and is prone, on the other hand, to create new ectopic centers. Also similar to quinidine, the maximum effect is observed clinically and electrocardiographically two to four hours after an oral dose. Neither the blood levels nor cumulative characteristics have been adequately investigated. However, the clinical impression prevails that in this respect both drugs are similar.

Undesirable extracardiac effects of procaine amide are nausea, vomiting, headache, and diarrhea. These occur with distressing frequency as the oral dose exceeds 4 Gm. daily. In cardiac action this is equivalent to only 1 Gm. of quinidine. Accordingly, it appears that for effective doses oral procaine amide is more toxic than quinidine. Disturbances of hearing and of vision, which are so common with quinidine if doses exceed 2 Gm. daily, have not been observed with procaine amide. However, it is difficult to give equivalent doses of this drug orally. Many instances of hypersensitivity to procaine amide have been reported. These include, like quinidine, urticaria, dermatitis, agranulocytosis, aplastic anemia, fever, muscle pains and mental disturbances. Extrasystoles and ventricular fibrillation appear. However, a given patient often is only sensitive to one of these drugs. Since sensitivity to quinidine is so common, the availability of a substitute is of importance. When quinidine must be discontinued because of its side-effects in a given patient, procaine amide may be substituted without interruption of schedule. Occasionally the additive action of the two drugs on the heart achieves therapeutic success otherwise impossible.

In direct proportion to the rate of the intravenous injection, procaine amide reduces the blood pressure to shock levels. This is not seen with oral administration. Quinidine acts

similarly. Therefore, when the intravenous route is used with either drug, not only the electrocardiogram but also the blood pressure must be concurrently observed. The injection should be performed very slowly, over at least a period of five minutes. It should be emphasized that the intravenous route is only rarely indicated. With the exception of unconscious patients and those unable to ingest medicines, oral administration is preferable.

The treatment of cardiac arrhythmias is often of great importance. False confidence in the safety of a drug can lead to its excessive use. It is, therefore, imperative to correct the erroneous impression that procaine amide is more effective and safer in the treatment of ventricular arrhythmias than quinidine. It is claimed that procaine amide may be effective when quinidine fails, but it is not always realized that acute ventricular tachycardias vary in their stability. Others overlook the additive effect of procaine amide given immediately after quinidine. Controlled investigations have failed to produce sufficient evidence for the superiority of procaine amide. On the other hand, occasionally ventricular tachycardias following acute coronary occlusion fail to respond to quinidine even if given in the largest permissible doses. In such instances, one occasionally obtains a prompt response from procaine amide.

Potassium, injected intracardially, has been known for almost 50 years to abolish ventricular fibrillation. On the other hand, an intravenous injection of potassium may readily induce fibrillation. Since hypokalemia is now recognized in a great variety of conditions and potassium salts, administered intravenously, are often recommended, extreme caution must be exercised. Even therapeutic doses of potassium salts given orally may cause A-V block with irregular ventricular complexes, supraventricular tachycardias or auricular standstill.[35] Renal function should be normal if potassium salts such as potassium chloride or acetate are employed. Many investigations have demonstrated that the diseased myocardium contains less potassium than normal cardiac muscle.[18, 39] The low potassium content may be a causal factor in the propensity of the diseased myocardium to develop tachysystolic centers, particularly following digitalis. This is suggested by the readiness with which oral doses of potassium inhibit such arrhythmias. The potassium content of the heart muscle of dogs following toxic doses of digitalis was found markedly diminished.[4]

Fagarine. The scarcity of quinidine during the Second World War stimulated research on other substances with antifibrillatory effects. One of the most interesting new drugs is fagarine, derived from a plant of the Argentine.[7] It appeared effective and nontoxic in animal experiments[28] but the clinical results were disappointing. It has the unfortunate tendency to induce ventricular fibrillation. In a limited experience with fagarine several instances of ventricular fibrillation occurred and the drug was abandoned.[32]

Atabrine, an antimalarial drug, is chemically unrelated to quinidine but has many similar actions. It inhibits cholinesterase, paralyzes the vagal fibers, depresses excitability and may abolish arrhythmias. So far, however, it has been found effective only in paroxysmal arrhythmias. The absence of a therapeutic effect in chronic fibrillation raises the possibility that the acute attacks of tachycardias or fibrillation in which the compound was apparently effective might have disappeared spontaneously. The drug (0.4 to 0.6 Gm.) is dissolved in 10 cc. of a 1 per cent solution of Novocaine and is injected intramuscularly.[10, 37]

Barbiturates distinctly reduce the propensity of the heart to develop arrhythmias. The excitability of the heart is diminished and extrasystoles caused by epinephrine, cyclopropane and other agents appear less frequently, in diminished numbers or not at all.[8, 20]

Acetylcholine and other choline derivatives play an important part in normal and abnormal stimulus formation. According to Burn and his school, the synthesis of acetylcholine within the cell plays an important part, as a "local hormone," in the normal automaticity of the heart.[3] While in certain doses, ectopic stimulus

formation is inhibited, these substances also initiate heterotopic stimulus formation and may cause flutter and fibrillation.

According to Dawes,[6] quinidine and procaine preparations abolish arrhythmias because of inhibition of the synthesis of acetylcholine and Burn[3] believes that procaine and quinidine exert their effects by competing with acetylcholine or epinephrine.

Comparative investigations led DiPalma and Lambert[9] to stress the importance of the presence of a methoxy group in antifibrillatory compounds. Dawes pointed out that the majority of drugs exhibiting a quinidine-like action contains an aromatic group joined to a basic group by an ester, ether or carbinol linkage. The antifibrillatory and anesthetic action of certain drugs show a good correlation.[6] This research may point the way to the discovery of new synthetic compounds.

Extrasystoles

Extrasystoles appear if impulses spreading over the heart elicit in a cell or a small group of cells (the center) more than one discharge. The supernormal phase which makes it possible, to "pick up" impulses from a subthreshold background certainly plays a smaller part in the genesis of extrasystoles than is often believed. In the mammalian heart, the phenomenon of the supernormal phase is found only under certain special conditions while extrasystoles persist in some patients for years and are abolished only with difficulty.

Extrasystoles vary greatly in significance. Usually they cause no symptoms. An occasional patient may suffer acutely, for each extrasystole provokes a short period of anginal pain, vertigo or annoying cough; the impact of the sudden irregularity on the psyche of the patient may be great. Most extrasystoles are harmless, but occasionally an extrasystole arriving during the last part of systole and earliest part of diastole (the critical or vulnerable phase) may lead to ventricular fibrillation.

Most extrasystoles seen in practice occur in persons with healthy hearts, but in other instances they constitute important evidence of heart disease or drug toxicity. Treatment of extrasystoles is indicated when they cause significant symptoms or may be the forerunners of more serious arrhythmias.

The presence of asymptomatic extrasystoles should not be mentioned to the patient. For the symptomatic type, avoidance of tobacco, correction of constipation and other simple measures may help. Often informing the patient of the harmlessness of his sensations induces him to forget his complaints. When symptoms are distressing, a careful and sympathetic explanation to the patient and administration of quinidine are advisable.

Variform ventricular extrasystoles denote organic heart disease. They may represent an early sign of coronary sclerosis; they may occur only on effort and be recorded during an exercise test; or they may appear at rest or during an attack of anginal pain. They are occasionally precursors of ventricular fibrillation just as auricular variform extrasystoles may foreshadow auricular fibrillation. They should be treated with quinidine.

Extrasystoles are quite common in acute myocardial infarction. In animal experiments involving ligation of a coronary artery, they are precursors of fibrillation and we assume that this holds for man as well. Accordingly, a determined effort should be made to suppress them or at least to decrease their frequency. Quinidine is the drug of choice with procaine amide as an acceptable substitute. Quinidine sulfate, 0.2 Gm. every six hours, is the usual initial dose. If the extrasystoles persist, the dose is increased. Usually therapy is effective. Some investigators claim that their animal experiments indicate that quinidine did not change or even increased the mortality rate. The fact that quinidine was administered intravenously in large doses in these experiments and caused respiratory standstill or diastolic arrest of the heart is probably responsible for the adverse results. These cannot supplant the mass of evidence, both clinical and experimental, in favor of quinidine. We strongly recommend the use of quinidine in every case of myocardial infarction with ventricular extrasystoles.

Digitalis usually abolishes extrasystoles provided the drug did not originally induce them.

This holds for normal hearts as well as for diseased ones. If the heart is healthy, even large, sublethal doses of digitalis do not induce extrasystoles. However, in some abnormal hearts it does so readily. Digitalis-induced extrasystoles are characteristically variform and continued exhibition of the drug may produce dangerous ventricular tachycardias and even ventricular fibrillation. Occasionally, even a dose smaller than the therapeutically effective one will induce extrasystoles. If the drug is urgently needed, the dilemma is solved by continuing small doses of digitalis (not more than 0.1 Gm. of the standardized leaf daily) and at the same time examining the patient twice daily before each dose. Should the frequency of the variform ventricular extrasystoles increase, the drug must be stopped. It is extremely doubtful if one form of digitalis will succeed where another has failed in such a case. Because digitalis extrasystoles are common in hearts with certain organic lesions such as the markedly dilated and failing heart of rheumatic mitral lesions, and because they are rare in other lesions, lack of potassium in the heart muscle fibers may well be responsible for their appearance. Potassium chloride and potassium acetate, given orally in the amount of 6 to 10 Gm. daily, actually abolish such extrasystoles,[25] but this therapy is rarely necessary. Occasional extrasystoles or bigeminal rhythm caused by digitalis disappear within a few days or several weeks after the drug is discontinued. Quinidine administered orally is of value in "preterminal" ventricular tachycardias caused by digitalis. An intramuscular injection of 0.25 Gm. of a suitable quinidine preparation[5] has been found to be life saving.

The appearance of digitalis extrasystoles following the injection of a mercurial diuretic has also been attributed to potassium loss during the diuresis. We consider, however, that the redigitalisation phenomenon is a more important etiologic factor.

Extrasystoles arising during digitalis therapy but not variform need not interdict digitalis. Careful observation is in order, however, for if they increase unduly or become variform the drug must be stopped.

Variform ventricular extrasystoles occur during anesthesia with cyclopropane. Ordinarily they are transient so that it is unnecessary to treat them actively. Occasionally ventricular tachycardia ensues and rarely ventricular fibrillation ultimately develops. Though many factors have been accused of favoring the appearance of extrasystoles during this type of anesthesia, the mechanism remains obscure. Anoxia and especially the use of sympathomimetic agents such as epinephrine should be avoided. Experimentally, the combination of cyclopropane plus epinephrine is a favorite method for inducing ventricular fibrillation. Apparently atropine and barbiturates prevent, to some extent, ventricular extrasystoles during anesthesia. The most publicized preventive agent has been intravenous procaine hydrochloride, but its alleged success is difficult to reconcile with its ineffectiveness under controlled conditions. Usually a definite action is obtained only when the doses are so large that neurologic toxicity is seen.

Extrasystoles are almost invariable during cardiac catheterization and cardiac surgery. They arise when the inner or outer layers of the heart are irritated. Contact with the heart of almost any blunt instrument, particularly if the instrument is of cold metal, may produce extrasystoles. Preventive treatment with quinidine or similarly acting drugs may diminish, but not entirely abolish their occurrence. During intubation, the catheter is to be withdrawn or pushed forward when extrasystoles appear in the electrocardiogram. Usually they then disappear. During cardiac surgery, the finger is left in the orifice of a valve as briefly as possible, and contact between heart muscle and cold instruments is minimized. Instillation of drugs into the open pericardium certainly is no less effective in influencing extrasystoles than medicine administered by injection since drugs are absorbed from the pericardial sac with the greatest speed.

Paroxysmal Tachycardias

These arrhythmias have such a great variety of clinical and electrocardiographic features that no two patients are identical. Many repre-

sent an occasional harmless attack in a healthy person; others are dangerous "preterminal" tachycardias which end in ventricular fibrillation. A paroxysmal tachycardia with a slow rate usually causes no symptoms. Rapid rates, however, particularly in elderly patients, may cause shock, anginal pain or congestive failure. Even hemiplegia and peripheral gangrene have been reported.[40] Pulmonary edema is not rare.

The subjective sensation of a racing heart almost always induces a great deal of anxiety so that reassurance is urgently needed. Before treatment the nature of the tachycardia should be determined with the aid of the electrocardiogram whenever possible. This is important because the significance, prognosis and treatment depend on whether an auricular or a ventricular type is present. In most patients therapy can be postponed until the tracing is taken and read.

One should always try to end the attack by producing one of the vagal reflexes before using drug therapy. This applies also to ventricular tachycardia for occasionally carotid pressure is successful even in this type. If done expertly, the production of vagal reflexes will stop about 50 per cent of the attacks of auricular tachycardia. The patient should be supine; cardiac action should be observed by auscultation. Carotid pressure and not carotid massage should be performed. Pressure on the right side is somewhat more effective than on the left. The pressure should be applied at different levels in order to make sure that the carotid sinus has actually been pressed upon; only this structure contains the receptors specific for the reflex. The pressure should not be exerted longer than 10 to 15 seconds. It is discontinued as soon as the tachycardia stops.

We do not press on the eyeball since upon two occasions we have observed detachment of the retina following this maneuver in patients with myopia. Induction of nausea and vomiting is often successful. The least obnoxious method for accomplishing this is to have the patient thrust two of his fingers into his throat. The use of ipecac is less pleasant and apomorphine should be prescribed only by those physicians who have injected this drug into themselves.

Other maneuvers which are successful at times are compression of the abdomen, Valsalva maneuver, sudden deep inspiration with holding of the breath and bending forward.

In regard to drug therapy there are few disturbances in which the rule "primum non nocere" is so often neglected as in paroxysmal tachycardia. The literature is replete with reports of sudden deaths in this usually harmless condition after an injection of acetylcholine, Mecholyl, neostigmine, epinephrine, quinidine, quinine, procaine amide and other substances. It is not uncommon for the doctor rather than the patient to become unduly alarmed and fling common sense to the winds. In the vast majority of cases even an attack lasting several days is well tolerated. Many patients feel only a peculiar sensation rather than palpitation.

Intravenous quinidine abolishes most attacks speedily, often within seconds. This therapy is warmly recommended despite repeated, emphatic and thoroughly justified warnings in the literature that sudden death from cardiac standstill or ventricular fibrillation may immediately follow the injection. A physician experiences great satisfaction if his injection stops an attack within seconds and without any side-effect. This happens in a few patients. In the next one, however, collapse and sudden death may ensue promptly. One can hardly overemphasize the danger associated with the intravenous use of this drug.

If the tachycardia has caused anginal pain or shock, immediate relief is indicated. An intravenous injection of digitalis or strophanthin is the wisest move. This is advised even in the presence of ventricular tachycardia, although we realize that this is contrary to the prevailing opinion. Of course, one must first make sure that digitalis did not cause the tachycardia. Carotid pressure often will abolish the tachycardia after the administration of digitalis although it failed before the injection. One may use 0.4 mg. of digitoxin or Cedinalid or 0.25 mg. of ouabain or Strophosid. Not rarely 20 cc. of a 20 per cent solution

of magnesium sulfate injected intravenously will stop the tachycardia. In patients with shock from a recent myocardial infarction we prefer the intravenous injection of digitalis or strophanthin.

In the vast majority of patients, when there is no urgency, the method of choice is quinidine by mouth. The first and second doses of quinidine (0.4 Gm.) are given one hour apart and are followed by 0.2 to 0.4 Gm. every two hours until the attack subsides.

The situation may be serious in those rare patients who do not respond to the vagal reflexes, to digitalis, to quinidine or procaine amide. This happens particularly in patients with fresh myocardial infarction. Such patients may die because of the tachycardia. A serious problem is also presented by the paroxysmal tachycardia complicating pregnancy when large doses of quinidine are contraindicated. The tachycardia disappears soon after the delivery.

If attacks of paroxysmal tachycardia occur frequently, prophylactic therapy with quinidine is the procedure of choice. The dose is adapted to the requirements of the patient.

Flutter

Auricular Flutter. Of late the justification for separating flutter from paroxysmal tachycardia has become questionable for both originate in a tachysystolic center.[27] The other differentiating criteria are not absolute. Carotid pressure frequently abolishes paroxysmal tachycardia but never flutter. It may even increase the flutter rate. In animals, however, flutter may be occasionally suppressed by vagal stimulation.[30] The response to vagal stimulation is not entirely a function of rate for in some patients with a tachycardia of 250 per minute carotid pressure may be successful.[40]

Brief attacks of paroxysmal flutter are treated with quinidine in the manner already described for paroxysmal tachycardia. If the attacks recur frequently the drug should be given every day as a prophylactic.

Opinions are divided as to the best therapy for flutter that has lasted more than a few days. It is agreed that such patients should be treated in the hospital because they require careful supervision. Either digitalis or quinidine can be used and there is no accurate guide which is best for a given patient. Most cardiologists favor the use of digitalis. Flutter is sometimes replaced by sinus rhythm but usually it is converted into fibrillation. Digitalis is best administered in the form of digitoxin, approximated 0.6 mg. daily for one or two days. As soon as fibrillation appears, the dose is reduced and a smaller maintenance dose is given. Usually one attempts to convert fibrillation into sinus rhythm with quinidine. Others prefer administration of quinidine from the start. During quinidine therapy, the ventricular rate may temporarily increase. This results from two mechanisms: (1) a decrease of the auricular rate allows the conduction of more stimuli to the ventricle and (2) the vagolytic effect of quinidine improves A-V conduction. There is no substantial evidence that the administration of digitalis before quinidine ameliorates this complication; digitalis slows A-V conduction mainly through increased vagal tone. The clinical consequences of a change from 3:1 or 2:1 block to 1:1 rhythm are, however, usually negligible in spite of a threefold increase of the cardiac rate.

The program of treatment is guided by the condition of the patient and the heart. Digitalis is used from the start when shock or severe anginal pain is present, after acute myocardial infarction with poor heart sounds and low blood pressure, in congestive cardiac failure, or with a very high initial ventricular rate.

If the general condition is good, some prefer to start with quinidine. The dosage is the same as has been described, since the primary purpose is identical for all tachysystolic arrhythmias; namely, to obtain a blood concentration adequate to suppress the tachysystolic focus. If a sudden rise in ventricular rate occurs, one should continue to administer quinidine. The additional quinidine will lower the ventricular rate either by decreasing the rate of the tachysystolic center or by decreasing the A-V conduction through its direct action on the A-V node and bundle. The danger of embolism with restoration of sinus rhythm is less than in fibrillation since the "fluttering" contractions of the auricles tend to prevent

thrombus formation in the auricles. There is no advantage in administering quinidine by intramuscular injection since no significantly higher blood levels are obtained by this method than by oral administration. The therapeutic levels are, however, reached earlier.

Some patients with auricular flutter have A-V block with a 4:1 or higher A-V ratio. Even after mild exertion, this block usually persists and prevents high ventricular rates. Under these circumstances therapy of the flutter itself is not indicated.

Procaine amide has not proved successful in the treatment of auricular flutter, probably because the required dosage is in the toxic range.

Occasionally, chronic flutter responds neither to digitalis nor quinidine. Antithyroid therapy is occasionally successful. At times flutter resists all therapy and constitutes a serious problem.

Ventricular Flutter. The separation of ventricular flutter from ventricular paroxysmal tachycardia is impossible. The treatment would be identical.

Fibrillation

Auricular Fibrillation. The treatment of paroxysmal auricular fibrillation is similar to that of paroxysmal tachycardia. Quinidine is employed for the attack if the attack is associated with severe exertion, during pneumonia, acute myocardial infarction and hyperthyroidism; it is also used prophylactically. In patients with congestive failure, a course of digitalis should precede quinidine. In some patients who have established auricular fibrillation with a slow ventricular rate, no therapy is indicated. Such patients often exhibit no other signs of heart disease. Mild exercise may increase the rate markedly;[2] under these conditions digitalis is indicated. Small doses, such as 0.1 Gm. of standardized powdered leaf daily, usually suffice.

Whether one should convert chronic fibrillation to a sinus rhythm constitutes a difficult problem. In the current wave of enthusiasm for conversion, one must recall that 2 to 5 per cent of all patients with chronic auricular fibrillation treated with quinidine experience either serious embolism or death.[21] The latter can be caused by ventricular fibrillation, cardiac standstill, cerebral embolism or respiratory failure. Accordingly, if the patient is not suffering appreciably from the fibrillation there is no need for aggressive therapy. The increased danger of embolism in chronic nontreated fibrillation is, of course, a real one. It is, however, by no means absent during sinus rhythm.

After the first instances of sudden death due to quinidine therapy were published, the original enthusiasm for this form of therapy subsided. It was emphasized that fibrillation of the auricle does not seriously affect the circulation if the ventricular rate is reduced to 80 beats per minute or less. Such slowing of the heart is actually possible in all patients unless rheumatic fever, hyperthyroidism or pulmonary embolism is present. The improvement that follows satisfactory control of the ventricular rate is certainly almost as great as that which follows conversion to sinus rhythm.

In recent years it has been shown, however, that in some patients with auricular fibrillation and a slow ventricular rate, restoration of sinus rhythm is accompanied by an increased minute volume and blood pressure and a fall in the venous pressure.[11, 15, 34] The activity of the auricles, therefore, is of greater importance in some patients than was formerly believed. Actually, this might be expected in patients with mitral stenosis where the contraction of the left auricle is helpful; however, in mitral stenosis with marked enlargement of the left auricle, an effective contraction is impossible even during sinus rhythm. In many but not all patients in whom sinus rhythm was restored, the clinical condition improved.[11, 17, 19, 22]

It is certain that the present enthusiasm for conversion of fibrillation will wane in the course of time just as it did in the early 1920's when quinidine was widely used for this purpose. Even anticoagulant therapy for 10 to 14 days before the course of quinidine does not prevent embolism although it may help in some cases. On the other hand, it introduces a new source of danger.

If it had been established that dangerous complications occur more often in fibrillating than in nonfibrillating patients, physicians

would be more willing to accept the risks involved in the use of quinidine. In any case it must be remembered that in patients with chronic heart disease such as mitral stenosis and coronary sclerosis, fibrillation recurs in 50 per cent within six months after successful conversion.

In brief, much of the hemodynamic disturbance caused by fibrillation can be corrected by digitalis alone with slowing of the ventricular rate. However, there is no doubt that a significant proportion of patients will benefit considerably from conversion. The latter however, is always a risky procedure and should be attempted only in selected cases in a hospital.

Definite contraindications to defibrillation exist in patients with mitral stenosis and a large left auricle; the danger of embolism attendant on conversion is especially great. On the other hand, if the patient is already manifesting multiple emboli, a course of anticoagulants followed by quinidine has been successful in preventing further emboli.

Conversion to regular rhythm is also contraindicated in patients with mitral stenosis who have had pulmonary edema or hemoptysis. Fibrillation seems to protect these patients from a recurrence of these incidents. Auricular fibrillation seems also to protect some patients with coronary sclerosis from angina pectoris; the reasons for this are not known.

Conversion of chronic fibrillation may be indicated in spite of all risks in the presence of intractable congestive failure.

All patients with fibrillation should be examined very carefully for the existence of hyperthyroidism.

The method of administration of quinidine has been discussed above. In most instances five daily doses are given at intervals of two hours. In one patient the dose of 2.66 Gm. (40 grains) was given five times daily without therapeutic effect.[33] Sinus rhythm will be re-established in about 80 per cent of the patients. After conversion has been achieved, it is important to prevent recurrence of fibrillation. It is often necessary to administer quinidine four times daily for an indefinite period.

Ventricular Fibrillation. This arrhythmia almost always causes death within a few minutes. Measures to abolish it in the experimental animal were recommended more than 50 years ago. The problem became clinically important with the advent of modern thoracic surgery. The principles of treatment of ventricular fibrillation differ considerably from those of the other cardiac arrhythmias. Since irreparable damage is sustained by the central nervous system after an absence of blood flow lasting three to five minutes, the need for immediate therapy is evident. To maintain some blood supply to the brain and to the myocardium the heart must be rhythmically compressed manually 40 to 50 times per minute. Simultaneously measures are invoked to terminate the fibrillation and supply oxygen.

While rhythmic compression of the heart is performed, intraventricular injection of an agent which will abolish the fibrillation should be made. The agent used should permit the resumption of rhythmic activity as soon as fibrillation subsides. Potassium chloride, although effective in abolishing fibrillation, is not advocated because it only rarely permits full recovery of the myocardium even if calcium is also used. Even if fibrillation disappears it often recurs.

Two agents which meet the requirements are procaine hydrochloride and electrical shock. Procaine hydrochloride introduced into the fibrillating ventricle in sufficient concentration stops the fibrillation. This compound is quickly hydrolyzed so that the myocardium can resume regular contractions within a few minutes. About 5 to 10 cc. of a 2 per cent solution are injected into the left and, if necessary, also into the right ventricle during the period of manual compression. The fibrillation can also be stopped by the application of electrical current.[1, 23, 38] The heart is placed between two large electrodes and an alternating current of 110 volt and 1.5 amperes is used. Special electrical units have been designed for this purpose.[16]

If cardiac inhibition with diastolic arrest is the cause of circulatory standstill the employment of procaine hydrochloride or the electric current is unnecessary. Therapy of cardiac arrest is discussed in the following

section. For resuscitation, rhythmic compression of the heart is needed in any case.

Disturbances of Conduction

Intra-auricular and intraventricular conduction disturbances do not lead to arrhythmias. Only on rare occasions does sinoauricular block cause cardiac standstill and require therapy. A-V block, however, occasionally causes disturbances demanding treatment.

No therapy is necessary for prolongation of the P-R interval. One should keep in mind that healthy individuals engaged in strenuous athletics may exhibit a P-R interval of 0.20 or 0.22 second with or without a bradycardia. Periodically dropped beats (Wenckebach phenomenon) as well as 2:1 or 3:1 A-V block do not require special therapy. Most patients with complete A-V block do not need treatment for the block itself; usually the centers in the ventricle take over the function of pacemakers satisfactorily. However, should these centers have an inherent rate too low for circulatory efficiency (24 beats per minute or less), it is necessary to treat the arrhythmia directly, since under these circumstances the heart is unable to increase the rate sufficiently on exertion. Patients with this condition experience marked dyspnea and weakness on slight effort. The administration of 0.032 Gm. of ephedrine three times daily increases the basic rate of the heart and improves the exercise tolerance. Usually, it is advisable for the patient to adjust his activities to his limited capacity.

The most serious complication of A-V block is the Stokes-Adams syndrome. Its prevention and treatment depend on the mechanics present in the particular case. Often the syndrome is caused by cardiac standstill when partial A-V block becomes complete and the ventricular pacemakers are tardy in taking over. In rare instances of permanent A-V block, cardiac standstill may result from an abnormality in the lower pacemakers. In still other cases of A-V block, the appearance of numerous ventricular extrasystoles or tachycardia or even short attacks of ventricular fibrillation interfere with cardiac action. It is not unusual for a patient to exhibit one mechanism at one time and the other at another time, or even tachycardia and standstill in rapid succession. Only an electrocardiogram obtained during an attack permits one to recognize the mechanism of a particular attack. The same disease, often bilateral bundle branch block, which causes the A-V block may lead to the formation of centers rapidly firing impulses. It may be assumed that the excitability of centers beyond a block is increased (Wedensky facilitation).

Since the therapy for Stokes-Adams attack due to one mechanism is harmful when the other mechanism is present, the task for the physician is not easy. The administration of drugs should be postponed until the mechanism of the attacks has been determined with the aid of the electrocardiograph.

To prevent Stokes-Adams attacks during the change-over from partial to complete A-V block, the establishment of permanent complete block by digitalis has been recommended. During an attack of cardiac standstill, the best treatment consists of mechanical stimulation of the heart by punching the chest vigorously with the fist. Ephedrine aids in preventing these attacks. Intracardiac injections have little justification; epinephrine may lead to ventricular fibrillation. If an intracardiac injection is undertaken, caffeine salts are less dangerous. The mechanical stimulus of the needle often suffices to awaken the automaticity of the ventricles.

When ventricular tachycardia or fibrillation causes circulatory standstill, it would seem logical to use quinidine or procaine amide. Experience shows, however, that this is dangerous; quinidine may cause ventricular fibrillation in such cases. Most examples of brief ventricular fibrillation reported in the literature have occurred in patients with complete A-V block who received quinidine.

Aminophylline suppositories appear to have some clinical merit in all forms of Stokes-Adams attacks probably through beneficial action on muscular metabolism. Therefore, this therapy is permissible even when an accurate diagnosis is impossible or where cardiac standstill and tachycardia succeed each other.

Complete A-V block following myocardial infarction requires no therapy and may be a welcome complication. The resulting bradycardia usually improves the relation between oxygen need and oxygen supply of the heart. A fall in blood pressure and pulmonary congestion may occur when the bradycardia is replaced by normal rhythm with an increased rate. The administration of oxygen and of suppositories of aminophylline is indicated.

The use of atropine in heart block, so popular a few years ago, is not justified. With increase in the auricular rate the degree of heart block may be increased and partial change into complete block.

Employment of digitalis in patients with partial heart block as well as in those with complete block should follow the rules that apply to all cardiac patients. When decompensation and myocardial failure are evident, digitalis is indicated. Large doses should not be used, that is, not more than 0.2 Gm. of digitalis daily, and the patient must be watched carefully.

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CLINICAL CONFERENCES

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Congestive Heart Failure Induced by Primary Systemic Amyloidosis

A Diagnostic Problem

Arranged by RAYMOND D. PRUITT, M.D., GUY W. DAUGHERTY, M.D., AND JESSE E. EDWARDS, M.D.

CONGESTIVE heart failure occurs commonly in males past 45 years of age as a consequence of coronary sclerosis associated with myocardial infarction or with hypertension. The clinical evidences of coronary sclerosis are not always identified readily in patients so afflicted, and this not uncommon basis for congestive heart failure of obscure etiology is not, to be sure, the only cause of such failure. To place all cases of congestive failure for which no cause is evident in the category of "arteriosclerotic heart disease" is to admit a lack of diagnostic sensibilities and to practice an indolent and erroneous form of medicine.

Report of Case. The patient whose problems are to be reviewed in this conference was first examined by a member of the staff of the Mayo Clinic in May, 1939. At that time the patient was 36 years old and came for investigation and treatment of pain in the lower portion of his back. This pain had begun following an accident. Examination of his heart was carried out at this time with negative results. His blood pressure was 112 mm. of mercury systolic and 76 mm. of mercury diastolic.

He was next examined at the clinic on April 21, 1952, at the age of 49 years. He reported that on January 30 he had experienced an episode of pain localized over the anterior aspect of the left side of his chest. This pain had persisted in severe form for 30 minutes and in milder intensity for the next 24 hours. He described the distress as of a sharp, excruciating character which took his breath away. Its severity was of an order established by the patient as the worst he had ever had. However, he did not consult a physician at this time and, following subsidence of the pain, he felt reasonably well and continued in his work as a maintenance man in a hotel. Three or four days prior to his examination on April 21 he had noted increasing dyspnea associated with exertion and a pitting type of edema had developed over the lower legs and ankles. Blood pressure readings were 90 mm. Hg systolic and 70 mm. Hg diastolic.

A physical examination made on April 21 disclosed no abnormalities other than edema of the lower extremities and a cardiac rate of 96 beats per minute.

Laboratory studies were productive of the following information. Specific gravity of the urine was 1.008 on one occasion and 1.006 on another. Albuminuria was graded 2 and the test for Bence Jones protein was negative. Microscopic study of the urine gave a negative result. The concentration of urea in the blood was 24 mg. per 100 cc. and of serum proteins, 5.10 Gm. per 100 cc., of which 3.67 Gm. was albumin and 1.43 Gm. was globulin. The sedimentation rate of erythrocytes was 29 mm. per hour by the Westergren method. Hemoglobin concentration in the blood, erythrocyte and leukocyte counts, and differential blood counts were within the limits of normal. The result of a serologic test for syphilis was negative. The chest x-ray disclosed no pulmonary pathologic condition. The transverse diameter of the heart was regarded as being at the upper limit of normal (fig. 1).

Further studies were advised but the patient chose to proceed with a program of treatment which included moderate restriction of his intake of salt and an appropriate dose of digitalis. His dyspnea subsided and his edema disappeared. However, he returned on June 3, 1952, to report that in spite of maintenance of therapeutic measures he had recurrence of edema, attended by dyspnea on mild effort, but no orthopnea. Findings on physical examination were unchanged except for the observation

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that the liver was palpable 2 cm. below the right costal margin when the patient inspired deeply.

On July 22, the patient weighed 169 pounds (about 77 Kg.), an increase of 15 pounds (about 7 Kg.) over his weight on June 3. His dietary intake of sodium had been restricted during the interval. Digitalis had been taken regularly until June 16.

On July 22, he was admitted to the hospital. Principal therapeutic measures included reinstitution of treatment with digitalis, administration of a mercurial diuretic at intervals of two or three days and of a diet containing 130 Gm. of protein and approximately 0.9 Gm. of sodium. On this regimen the patient's weight declined from 169 pounds to 141 pounds (about 64 Kg.) during a period of 14 days.

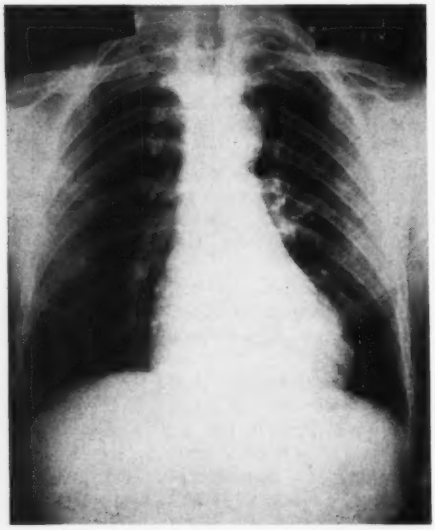


FIG. 1. Roentgenogram of the chest made April 22, 1952.

Between August 4, the date of his dismissal from the hospital, and September 15, the patient's weight gradually increased to 193 pounds (about 88 Kg.) in spite of continuation of all measures which could be applied to curtail accumulation of edema. Because of anasarca, easy fatigability, weakness and dyspnea on exertion, he was readmitted to the hospital on Sept. 26, 1952. On the morning of his fourth day in the hospital, he became very dyspneic and cyanotic while moving about his room. He was helped into his bed. His symptoms persisted and he died within a period of five minutes.

In summary, this patient's illness was initiated by an episode of severe thoracic pain. This was followed in three months by the development of edema and dyspnea on exertion which disappeared for a month under treatment with digitalis and restricted ingestion of sodium. Thereafter efforts to control the patient's edema became less and less effective and he died, not unexpectedly but rather abruptly, 9 months after the onset of his illness.

MODERATOR: Dr. Pruitt, would you open the discussion of the case?

DR. R. D. PRUITT: Two problems appear to require some elaboration. First, of what significance was the episode of pain in January, 1952, in the development of this patient's illness? Second, what significance should be attached to the preponderance of edema over all other manifestations of disability in the evolution of his disease?

With respect to the first question, it may be noted that the distribution and quality of the patient's pain was not altogether typical of that distress which is commonly associated with the occurrence of myocardial infarction. But it was severe. Certainly myocardial infarction is not to be excluded as a possible occurrence at that time. Did this patient have similar pain in milder form precipitated by exertion either before or after this major attack?

MODERATOR: So far as we know, he did not.

DR. PRUITT: May we review at this time such electrocardiographic evidence as is available? (See fig. 2.)

The first tracing was made on June 4, 1952, some six months after the episode of pain and after treatment with digitalis had been instituted. One is impressed immediately by the low amplitude of the QRS complexes in leads I, aV_R and aV_L. Neither in the extremity leads nor in the precordial leads is there an aberration in QRS configuration which affords specific evidence of a myocardial scar. Significance of the QS deflection in lead aV_L is limited, especially since there is no R wave in lead aV_R. The R wave in the precordial leads is absent in V_1 and of low amplitude in the remainder of the precordial leads. However, at no point is a Q wave discernible. The RS-T segment depression in standard leads II, III, extremity lead aV_F and precordial leads V_5 and V_6, as well as the RS-T elevation in aV_R, presumably may be ascribed to the effects of digitalis.

In the electrocardiogram recorded six weeks later (July 23, 1952) the form of the complexes in lead V_5 is noteworthy inasmuch as a notch is present in an R wave of very low amplitude.

Unfortunately, records were made from only three precordial positions.

If a myocardial scar is responsible for the peculiarities of this electrocardiogram, its location almost certainly would be in the lateral wall of the left ventricle. I would conclude, however, that both the historical and electrocardiographic evidence of myocardial infarction are inconclusive and that the most substantial reason for suspecting that this patient's illness and death were related to postinfarction congestive heart failure is the frequency of this type of illness as compared with other pathologic processes producing a similar clinical picture in men of 50 years.

May I propose that Dr. Daugherty discuss the second question which was raised, namely what significance should be attached to the preponderance of edema over other manifestations of disability in the evolution of the patient's disease?

DR. G. W. DAUGHERTY: I saw this patient on June 4, 1952. He was moderately edematous. He was continuing to work as a maintenance man in a hotel. This job required considerable walking and some lifting, so while he was aware of dyspnea it was not severe nor was he orthopneic. Urinalyses revealed albuminuria, grade 2 to grade 3, and the concentration of the total serum protein was slightly below normal. However, the reduction was greater rather than less in the globulin than in the albumin fraction. Several collections of urine over a 24-hour period showed the loss of protein to be about 0.1 Gm. per 100 cc. The urinary sediment contained a few hyaline casts and an occasional erythrocyte. The Bence Jones protein reaction was negative. The cardiac silhouette in a roentgenogram of the chest was enlarged and the venous pressure in the right antecubital vein was 14 cm. of water.

The occurrence of edema, without marked dyspnea, tended to draw attention away from a failing left ventricle as a cause of the patient's difficulty. Constrictive pericarditis seemed unlikely since there was no hepatic enlargement and no great elevation of the venous pressure. The urinary findings suggested kidney disease. It was my impression at the time that this patient had a specific renal lesion, either as a primary disease or in association with that heart disease which was causing the cardiac enlargement. I did not feel that the renal findings were to be explained on the basis of congestive heart failure. However, the evidence at the time was not satisfying for the diagnosis of the nephrotic syndrome as an explanation for the preponderant edema nor did subsequent urinalyses and determinations of serum protein

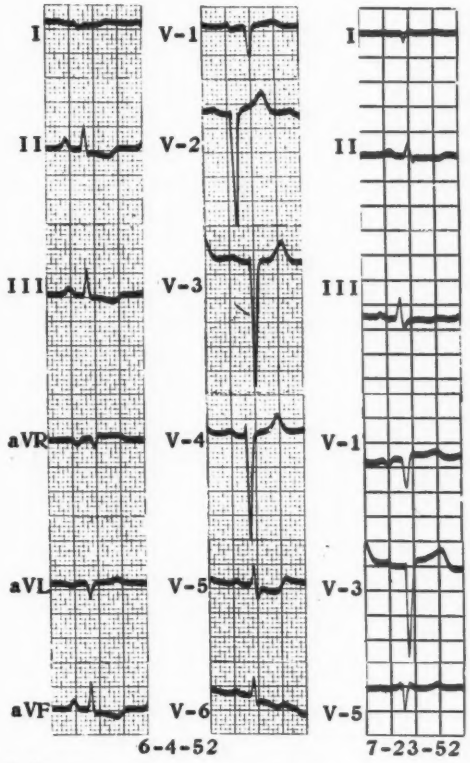


FIG. 2. Electrocardiograms. For discussion, see text.

values afford more convincing evidence of such a disorder. The lowest value for proteins in the serum was recorded on July 15, 1952, when it was 4.9 Gm. per 100 cc., of which 3.5 Gm. was albumin and 1.4 Gm. was globulin. The concentration of cholesterol in the plasma on this date was only 134 mg. per 100 cc.

Because of the combination of findings suggestive of renal disease and heart disease, I suggested that a Paunz test for amyloid be

performed. This was done on June 5, 1952, and the result was reported as negative.

DR. PRUITT: I do not understand why you were so confident that the patient had a specific renal lesion. Could not the findings on urinalysis and the altered concentration of proteins in the serum be encountered as effects of congestive heart failure on renal function?

DR. DAUGHERTY: Certainly that question should be raised. The presence of the abnormal findings in the urine could indeed be due to congestive phenomena in the kidney. However, in mild failure—and recall that this patient did not have hepatomegaly and was still working—I have not seen such changes in the serum proteins. Further, when there are significant congestive changes in the kidneys the concentration of urea in the blood tends to be slightly elevated. In this patient this concentration was 16 mg. per 100 cc. of blood and a urea clearance test, done shortly afterwards, revealed a result within the range of normal values.

May I suggest that Dr. M. W. Anderson continue the discussion inasmuch as he assumed certain responsibilities in the patient's care approximately at this phase of developments?

DR. ANDERSON: I saw this patient on July 28, 1952, approximately two months after Dr. Daugherty's initial observations. During this interval, certain significant developments had occurred. The patient's weight had increased to 169 pounds (about 77 Kg.), of which at least 30 pounds (about 14 Kg.) represented retained fluid. His liver, which had not been palpably enlarged at the time of the initial examination in April, was noted to descend 2 cm. below the right costal margin. A test of hepatic function by the Bromsulphalein method indicated retention of dye, grade 1 (10 per cent). Like Dr. Daugherty, I believed the evidences of renal and hepatic involvement were greater than could be accounted for on the basis of congestive heart failure as manifested in this case. There was no evidence of diabetes nor of cutaneous pigmentation to support the presence of hemachromatosis. The Paunz test was repeated on July 29, 1952, with negative results. The decision was made to proceed with needle biopsy of the liver and this was carried out by Dr. Stauffer on July 31. Examination of the tissue obtained disclosed findings typical of amyloid disease. A clinical diagnosis was made of primary systemic amyloidosis with involvement of the heart, kidneys and liver.

MODERATOR: Dr. Edwards, would you summarize the significant observations made at the time of necropsy?

DR. J. E. EDWARDS: The pathologic features in this case were those of primary systemic amyloidosis, with considerable widespread involvement of blood vessels, as well as heavy infiltration of most of the viscera, including the heart. Evidence of congestive cardiac failure was present in the form of edema of the legs, ascites (300 cc.), bilateral hydrothorax (1,000 cc. each side) and central hemorrhagic necrosis of the liver.

In the heart the infiltration by amyloid was suspected on gross morphologic examination, for fine granular elevations were found in the endocardium of both atria and in the atrioventricular valves. Gross sections of the myocardium revealed translucent, gray, speckled lesions measuring approximately 1 mm. in greatest dimension.

Microscopic examination of the heart revealed extensive involvement of the myocardium. In some regions this took the form of an increase in thickness of the reticulum fibers, brought about by the presence of amyloid (fig. 3*a*). In other regions this change was associated with atrophy of muscle fibers. In still other regions there were large masses of amyloid in which no muscle fibers remained (fig. 3*b*). Such regions were probably those which had been observed on gross examination of the myocardium. As in other organs, the myocardial blood vessels and surrounding stroma were greatly thickened with amorphous material, which was amyloid (fig. 3*c*). There were nodular accumulations of amyloid within the leaflets of the atrioventricular valves (fig. 3*d*).

In the lungs there was considerable involvement of the blood vessels and the alveolar walls. In addition, the mucosae of the small bronchi contained nodules of amyloid (fig. 3*e*).

The liver was only slightly enlarged; it

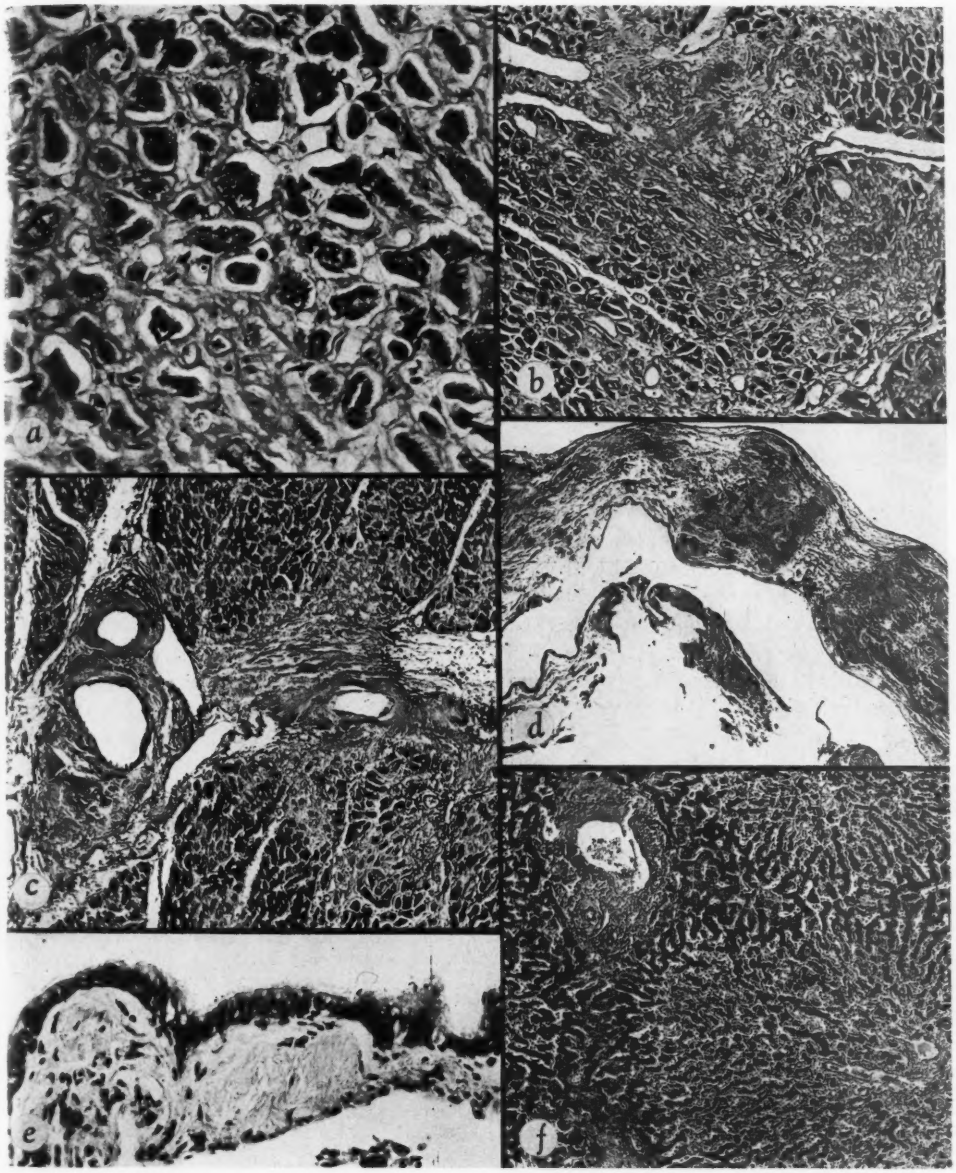


FIG. 3. Sections of heart stained with hematoxylin and eosin. (*a*) The myocardium. Thickening of basement membranes by deposition of amyloid. In areas of heavier infiltration there is atrophy of muscle fibers (×430). (*b*) Myocardium. Nodules of amyloid associated with disappearance of muscle fibers (×70). (*c*) Myocardium. Heavy infiltration by amyloid of blood vessels and surrounding stroma (×65). (*d*) Tricuspid valve. Nodular infiltration of valve leaflet with amyloid (×50). (*e*) Small bronchus. Nodules of amyloid beneath epithelium (×235). (*f*) Liver. In a portal area there is a slight degree of amyloid in the blood vessels and connective tissue. Also there is a picture of extensive central hemorrhagic necrosis (×65).

weighed 1,910 Gm. Of all the viscera, the liver contained the least amyloid. This material was almost entirely confined to the blood vessels and connective tissues of the portal regions. In relation to the parenchymal cords there was little amyloid. Examination of the liver also disclosed the changes of central atrophy, necrosis and hemorrhage, features attributed to cardiac failure (fig. 3*f*).

The kidneys were slightly enlarged. Together they weighed 440 Gm., which is approximately 150 Gm. heavier than the anticipated normal. The kidneys were of uniform size and were similar in appearance. Scattered, cortical, small, acute infarcts were present. Otherwise the cortices were of relatively thick pinkish-gray appearance. The pelvis, calyces and ureters were unusually resilient, and the mucosa contained foci of amyloid which gave to the surface a raised, speckled character resembling that of the lining of the atria of the heart (fig. 4*a*). On microscopic examination of the kidneys, nodular deposits of amyloid were found in the glomerular tufts (fig. 4*b*). The blood vessels throughout the organs, and the connective tissue and fat in relation to the pelvis, also were involved.

The thyroid gland was, for the most part, replaced by amyloid which was represented by infiltration within the blood vessels and in the stroma (fig. 4*c*).

On microscopic examination of the adrenal glands, amyloid was found deposited on the surface of the fat cells around the organs, in the capsule and in the blood vessels related to the capsule. The zona fasciculata and zona reticularis were particularly heavily infiltrated and this infiltration was associated with disappearance of parenchymal cells (fig. 4*d*).

Examination of the testes revealed amyloid deposited intramurally within the blood vessels and in the connective tissue supporting these (fig. 5*a*). None was found in direct relation to the seminiferous tubules.

In the gastrointestinal tract amyloid was found within the walls of blood vessels, and particularly striking was deposition of this material in the connective tissue of the tunica propria of the mucous membranes (fig. 5*b*).

There were striking nodular deposits of amyloid in the corium immediately beneath the epithelium (fig. 5*c*).

The tongue was heavily involved. This included deposition within the walls of the blood vessels and in the salivary glandular tissue of the tongue and among the muscle bundles (fig. 5*d* and *e*).

A submaxillary gland was heavily infiltrated, the degree of infiltration resembling that in the thyroid (fig. 5*f*).

The spleen was considerably involved, particularly the malpighian bodies and related blood vessels. The bone marrow was essentially normal.

Examination of the sciatic nerves revealed small amounts of amyloid within the walls of blood vessels related to the nerves and in an occasional area there was infiltration of the walls of blood vessels within nerve bundles.

MODERATOR: Dr. Daugherty, patients with systemic amyloidosis are said to develop a nephrotic syndrome. In your discussion you emphasized the absence in this patient of features prerequisite to a diagnosis of the nephrotic state. Have other patients with systemic amyloidosis exhibited the characteristic findings of the nephrotic syndrome or has that designation been applied loosely or mistakenly as it might have been in this case?

DR. DAUGHERTY: About a third of patients with renal amyloidosis develop certain nephrotic features. These include findings that range all the way from albuminuria with edema, to what one considers the full-blown picture of nephrosis: heavy albuminuria, massive edema, hypoproteinemia with reversal of the albumin-globulin ratio and elevation of the plasma lipids. Although there are instances of the full-blown picture, more frequently the patients seen are in the other category. Most certainly there are all gradations of the nephrotic picture, and it may worsen or improve at different times in the same case. Therefore, I would say the term is used loosely, but perhaps justifiably, to designate the patient with renal amyloidosis who has clinical features indicating a rather advanced stage of the disorder. In so far as I am aware amyloidosis of the kidney presents the same

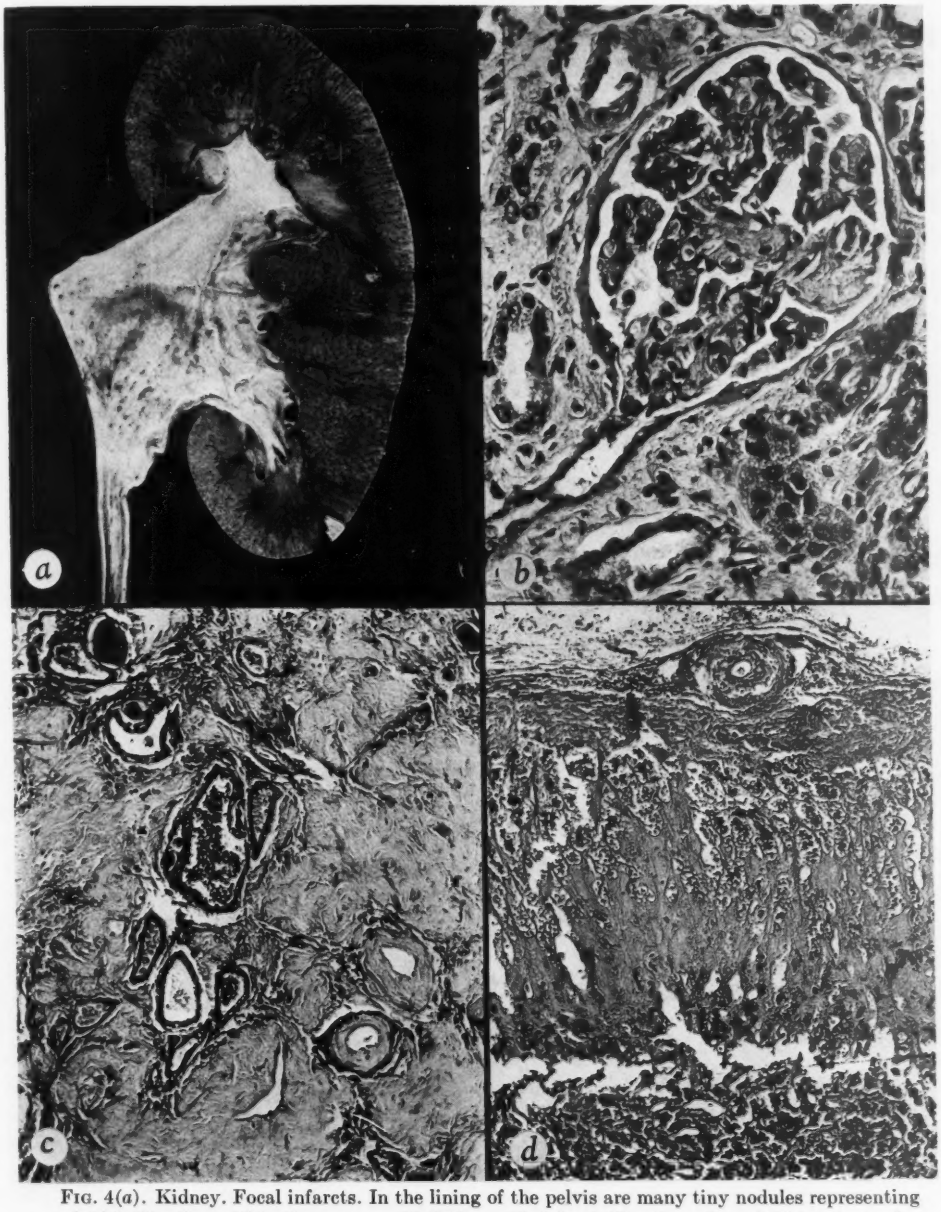


FIG. 4(*a*). Kidney. Focal infarcts. In the lining of the pelvis are many tiny nodules representing amyloid infiltration within the mucosa. (*b*) Kidney. Nodular infiltration of amyloid in glomerular tuft (hematoxylin and eosin; ×305). (*c*) Thyroid. Extensive infiltration in blood vessels and connective tissue by amyloid, leaving only isolated acini (hematoxylin and eosin; ×85). (*d*) Adrenal gland. Amyloid within the capsule and an associated blood vessel, as well as within the cortex. In the latter location the infiltration is associated with loss of parenchymal cells (hematoxylin and eosin; ×75).

picture clinically whether it be secondary, or so-called primary amyloidosis.

MODERATOR: Dr. Pruitt, was the electrocardiographic evidence in this case typical of amyloidosis?

DR. PRUITT: The role of the electrocardio-

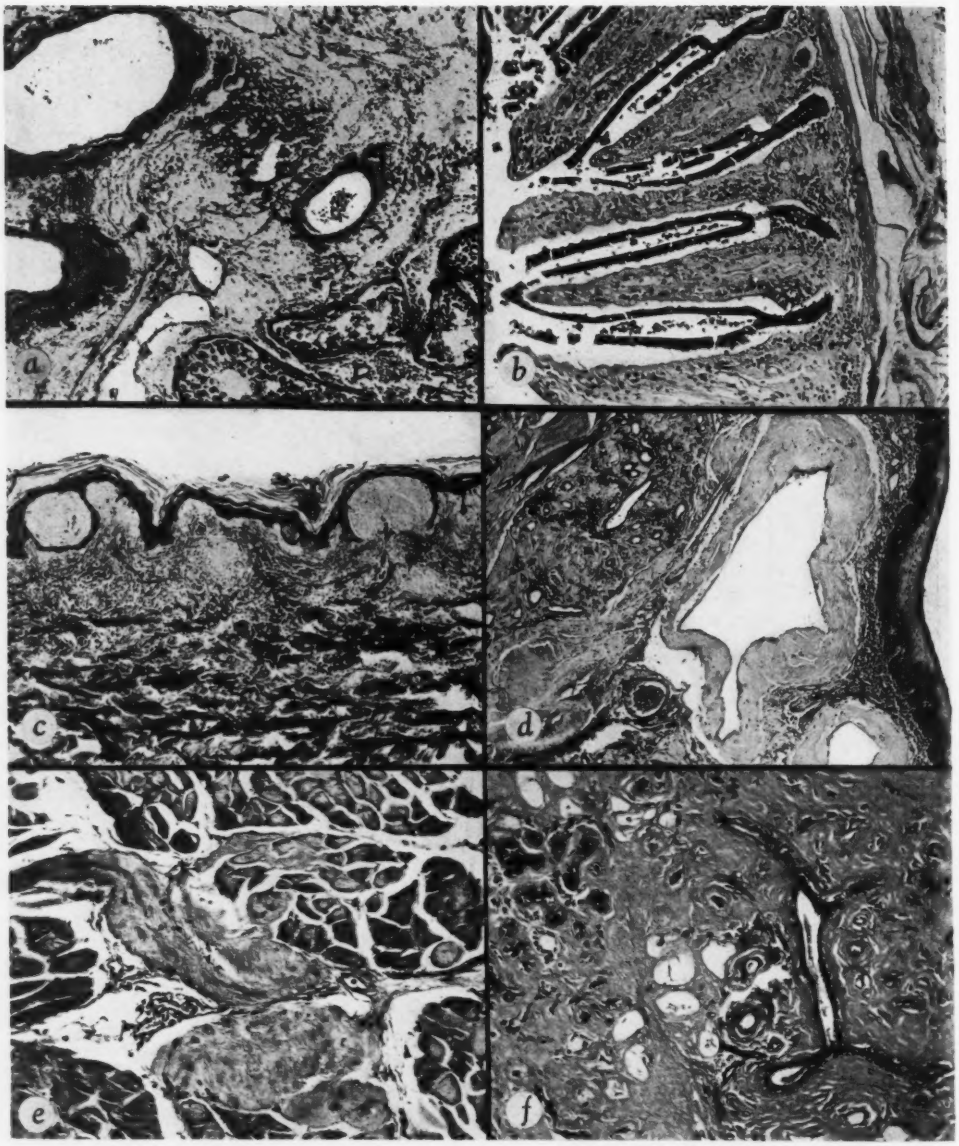


FIG. 5(*a*). Testis. Infiltration of blood vessels and surrounding stroma with amyloid (hematoxylin and eosin; ×90). (*b*) Jejunum. Heavy infiltration of tunica propria with amyloid (hematoxylin and eosin; ×85). (*c*) Skin of thorax. Nodules of amyloid beneath epithelium (Mallory's phosphotungstic acid-hematoxylin stain; ×75). (*d*) Tongue. A blood vessel immediately beneath the mucosa is heavily infiltrated with amyloid as is an underlying focus of salivary glandular tissue (hematoxylin and eosin; ×50). (*e*) Muscle of tongue. Nodules of amyloid (hematoxylin and eosin; ×115). (*f*) Submaxillary gland. Heavy infiltration with amyloid (hematoxylin and eosin; ×115).

gram in the diagnosis of cardiac amyloidosis is, at best, a supportive one. Study of the tracings obtained from 15 patients who had cardiac amyloidosis of various types led us here to conclude that definitive evidence of the disease cannot be had from the electrocardio-

gram. The existence in the standard limb leads of QRS complexes of small amplitude is a finding commonly encountered in the disease but, to be sure, not peculiar to it alone. The same may be said of the findings in the precordial leads, where the R waves in positions 4, 5 and 6 are unusually small. In summary, the electrocardiograms in this case were as suggestive of amyloidosis as an electrocardiogram is likely to become, yet they played a minor part in identification of the correct diagnosis.

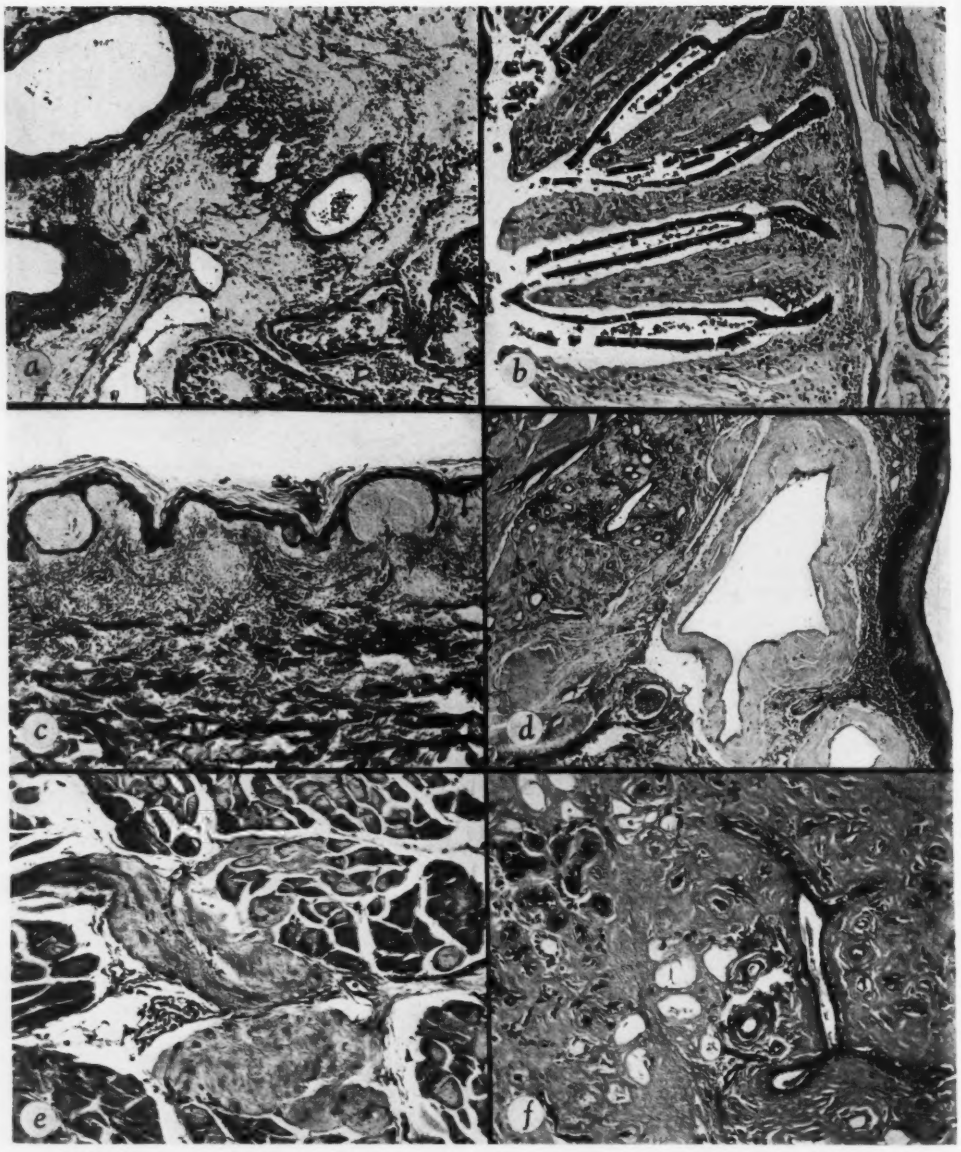
MODERATOR: Dr. Mann, on two occasions the Paunz test for amyloidosis gave a negative result in this case. Would you comment on the usefulness and limitations of this test? Could any refinements, however tedious, lead to improved efficiency of the test as a diagnostic measure?

DR. F. D. MANN: I cannot think of any technical refinement that would deal differentially with the basic fact that Congo red can leave the circulating blood of many persons whose bodies contain no amyloid just as rapidly as it can leave the bodies of many who have amyloidosis. This was rather well demonstrated in the series of 105 cases of secondary amyloidosis studied at Sea View Hospital. The diagnosis in each case was confirmed at necropsy. In 24 per cent of the cases in this series, rates of removal of Congo red from the blood stream had not differed appreciably from normal. For this reason, we here have preferred the Paunz test, in which complete removal of the dye from the circulating blood is the criterion of positivity, to methods which are called "quantitative" because the Congo red remaining in the blood stream is measured. One would expect an appreciable number of false negatives using this criterion. We have not encountered false positives, but cases have been reported by other observers in which complete removal of Congo red from the blood stream was observed and no amyloid was found at necropsy. Unfortunately, almost all data on the Congo red test concern its use in cases of secondary amyloidosis. The little information which is available on primary amyloidosis includes the highly discouraging observation that the amyloid in this condition often has no special affinity for Congo red.

MODERATOR: Dr. Stauffer, would you comment on your experiences with needle biopsy of the liver as an aid in the diagnosis of systemic amyloidosis?

DR. M. H. STAUFFER: It is well known that in secondary amyloidosis, biopsy of hepatic tissue usually will afford evidence sufficient to establish the diagnosis, since in most cases the liver is involved along with the spleen, adrenal glands and kidneys. In primary amyloidosis the myocardium, blood vessels, skeletal muscles and skin are predominantly involved, whereas the liver has been said by some authors to be seldom affected. Reports have appeared, however, of several cases of primary amyloidosis in which the principal clinical manifestations have been those of hepatic disease. These reports indicate that the liver may be severely involved in the primary type of this disease. This fact, along with many other peculiar aspects of amyloidosis, suggests that there is not always a clear-cut difference between the primary and secondary syndromes. Therefore, when my colleagues have asked me to attempt to secure evidence definitive of amyloidosis by biopsy of the liver of a patient who presents clinical features favoring the primary type of the disease, I have undertaken the procedure with some optimism. In the past two years I have secured hepatic tissue containing deposits of amyloid from seven patients, on whom preceding clinical studies had indicated existence of the primary type of the disease.

The Paunz or the Congo red test often gives a negative result in primary amyloidosis since, in this form of the disease, the amyloid has less affinity for Congo red than in secondary amyloidosis. This feature of the primary type of the disease makes the results of examination of tissue obtained for biopsy more critical in determining the diagnosis. When a patient does not have macroglossia or cutaneous lesions, it appears to me that the liver should be considered a fruitful source of tissue for microscopic study. This is especially true if that organ is enlarged and firm or if there are associated signs of hepatic dysfunction not



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readily accounted for by such congestive heart failure as may be present. If congestive heart failure is quite evident, then appropriate treatment should be instituted and maintained for several days prior to biopsy of the liver in order to lower the venous pressure as much as possible. There is a report in the literature of death occurring as a consequence of needle biopsy of the liver of a patient who had amyloidosis. This report, combined with the frequent presence of congestive cardiac failure among patients with amyloidosis, suggests that the risk of performing biopsy may be increased if individuals are afflicted with this disease. However, we here have now performed needle biopsy on nine patients who had amyloidosis without untoward incident; this series includes the seven patients already mentioned who had primary amyloidosis, and two additional patients who had the secondary form of the disease.

MODERATOR: Dr. Edwards, would you integrate this case of primary systemic amyloidosis with the general problem of cardiac amyloidosis?

DR. EDWARDS: Cardiac amyloidosis may be encountered as part of the three following conditions: Primary systemic amyloidosis, secondary amyloidosis and amyloidosis complicating multiple myeloma. In addition, deposition of amyloid may be restricted to the heart, the remaining organs failing to show deposition of this material.

Characteristically, as in the case here presented, primary systemic amyloidosis is associated with involvement of the heart, and in this disease congestive cardiac failure is not an uncommon cause of death.

In secondary amyloidosis cardiac involvement may be encountered at times, but this circumstance is relatively uncommon, the amyloid being deposited mainly in the abdominal viscera.

In approximately 20 per cent of patients who die from multiple myeloma, amyloidosis is an associated pathologic finding. While the deposition of amyloid may be considered secondary to the presence of multiple myeloma, the characteristics of its deposition simulate those of primary, rather than secondary, amyloidosis. In amyloidosis complicating multiple myeloma, therefore, cardiac involvement is a frequent occurrence.

Deposition of amyloid restricted to the heart has in recent years become recognized as occurring more commonly than was appreciated in the past. This manifestation of amyloid disease usually is limited to individuals in the decade of life from 70 to 79 years and beyond. While the degree of deposition in the usual case in which amyloid is confined to the heart is less than in cases of primary systemic amyloidosis, there are isolated cases in which heavy deposition occurs and in which congestive cardiac failure is attributable to this deposition.

SUMMARY

This conference has been concerned with a case of primary systemic amyloidosis in which death occurred in the course of severe, congestive heart failure. Major emphasis has been attached to the diagnostic problems which were posed by a patient so afflicted. If comments regarding treatment have been of limited extent, so have been the results of treatment when applied.

ABSTRACTS

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BACTERIAL ENDOCARDITIS

Donzelot, E., Bozec, J. M., Kaufman, H., and Escalle, J. E.: The Prognosis of Subacute Bacterial Endocarditis Treated by Antibiotics. Arch. mal. coeur **46:** 97 (Feb.), 1953.

The authors present a follow up study of 202 cases of subacute bacterial endocarditis caused by miscellaneous organisms and treated by penicillin and other antibiotics in the conventional manner. The over-all mortality was 24.25 per cent. Immediate mortality is especially high in the absence of bacteriemia, aortic endocarditis, and in the presence of congestive heart failure. An apparently healed case, in satisfactory condition, remains a cardiac patient who in the future may develop a recidivity due to reinfection, heart failure, or renal insufficiency. The risk of reinfection and renal failure is small (2.4 and 1.5 per cent respectively in the studied material), but heart failure is the decisive factor in the prognosis of successfully treated patients. In this series it developed in 60 per cent of the survivors within 3 to 60 months.

When severe cases are excluded from the statistics permanent recovery can be expected in 65 per cent of the treated cases. In the group of classic cases consisting of middle aged patients with an old rheumatic valvular lesion, without history of heart failure and with a positive blood culture, the chances of recovery are 83 per cent. More than 70 per cent of these patients remained alive and in good condition four to seven years after termination of the treatment.

PICK

BLOOD COAGULATION

Stefanini, M.: Mechanism of Blood Coagulation in Normal and Pathologic Conditions. Am. J. Med. **14:** 64 (Jan.), 1953.

In this scholarly seminar the author reviews concisely and thoroughly the mechanism of blood coagulation in normal and pathologic conditions. Individual factors playing a recognized role in the process of blood coagulation have been found in platelets, plasma, and serum. Platelets supply (1) the platelet thromboplastic factor which is indispensable for the activation of thromboplastin from an inactive plasma precursor; (2) platelet factor 1 which accelerates the conversion of prothrombin to thrombin, and is probably closely related to the "serum accelerator"; (3) platelet factor 2 which accelerates the

$$\text{fibrinogen} \xrightarrow{\text{thrombin}} \text{fibrin}$$

reaction; and (4) platelet factor 3 which opposes the activity of heparin. Platelets are also needed for clot retraction. Plasma supplies plasma thromboplastic factor, plasma thromboplastic component, prothrombin, prothrombinogen, calcium, and other materials. The various theories of blood coagulation are evaluated. All generally agree that agglutination of disintegrating platelets represents the initial step in the normal coagulation of blood. In this process activation of thromboplastin occurs. It supplies a vasoconstrictor principle which causes a prolonged, generalized state of vasoconstriction, thus reducing blood loss and favoring a firm anchoring of the fibrin clot. One or two factors besides thromboplastin and calcium are necessary for the optimal conversion of prothrombin to thrombin. Fibrin is considered active in that it absorbs thrombin on its surface and labilizes platelets in the manner of any rough surface, thus liberating more thromboplastin activator and contributing to the continuation of the autocatalytic reaction. The process of blood coagulation is a delicate unstable balance between positive and negative forces which multiple factors and conditions can easily influence. Problems of the fibrinolytic system still remain to

be solved. Antifibrinolysin activity may be increased in coronary thrombosis, thus theoretically inhibiting disposal of the clot by fibrinolysis. The same observation has been made in other thromboembolic conditions.

HARRIS

Owren, P. A.: Prothrombin and Accessory Factors. Clinical Significance. Am. J. Med. **14:** 201 (Feb.), 1953.

The author summarizes his studies leading to the isolation and identification of proaccelerin, accelerin, proconvertin, and convertin. Proaccelerin is the clotting factor discovered in 1943 which acts principally by increasing the velocity of the conversion of prothrombin to thrombin. Accelerin is the active principle responsible for this reaction. Proconvertin is another clotting factor first reported in 1947 and provisionally named cofactor V. Proconvertin is a prerequisite for thrombin formation under physiologic conditions. Proconvertin and thromboplastin do not act directly on prothrombin but first interact in the presence of calcium to produce the prothrombin-converting principle named convertin. Convertin is the first and the foremost prothrombin-converting principle produced during normal clotting. Without prior formation of convertin no thrombin will be elaborated under physiologic conditions. The proaccelerin-accelerin system enters as a secondary reaction. Accelerin and calcium cannot convert prothrombin to thrombin in the absence of convertin. Accelerin acts only in the presence of convertin, but its presence enormously accelerates the reaction.

Preparation of these principles in comparatively pure form and methods for quantitative determination are then discussed. A survey of the clinical significance of deficiencies in prothrombin and the accessory factors closes the review.

HARRIS

Johnson, S. A., and Schneider, C. L.: The Existence of Antifibrinolysin Activity in Platelets. Science **117:** 229 (Feb. 27), 1953.

The authors describe their work showing that platelets contain an antifibrinolysin. Under the conditions of their experiment, the platelet compartment contained approximately 70 per cent as much antifibrinolysin as was obtained from the plasma of the same sample of blood. This cannot be regarded as an exact quantitative statement but rather as a concept of an order of magnitude.

WAIFE

Peel, A. A. F.: Coagulation Time in the Selection of Cases for Anticoagulant Treatment. Brit. Heart J. **15:** 8 (Jan.), 1953.

In individuals with cardiac infarction, cardiac ischemia, and the coronary prodromal syndrome, the author attempts to differentiate those who must from those who need not be given anticoagulants. Differentiation is based upon a modification of Rosenthal's heparin retarded coagulation time. Sixteen minutes or less was regarded as an indication to use anticoagulant therapy. Second attacks were more frequent in those with accelerated coagulation time.

The mortality in the group with accelerated coagulation time, treated with anticoagulants, was 17 per cent compared to 13 per cent in the group with normal or prolonged coagulation time, treated without anticoagulants. Thromboembolic complications was the chief cause for this difference.

SOLOFF

CONGENITAL ANOMALIES

Howarth, S., and Lowe, J. B.: The Mechanism of Effort Syncope in Primary Pulmonary Hypertension and Cyanotic Congenital Heart Disease. Brit. Heart J. **15:** 47 (Jan.), 1953.

The authors present data obtained during attempts to produce effort syncope in two individuals with primary pulmonary hypertension, two with Fallot's tetralogy, four with patent ductus arteriosus, and one with a ventricular septal defect.

Syncope tends to occur after a variable period following exercise. This reaction correlates well with the gradual and progressive fall of systemic pressure after exercise. Simultaneous records of right heart and systemic blood pressures during an attack show acute right heart failure due apparently to the steep rise in pulmonary arterial pressure. Pallor and bradycardia are likewise present. A sudden fall in arterial oxygen tension or saturation may also be a factor in the mechanism of syncope.

SOLOFF

Broadbent, J. C., Wood, E. H., and Burchell, H. B.: Left-to-Right Intracardiac Shunts in the Presence of Pulmonary Stenosis. Proc. Staff Meet., Mayo Clin. **28:** 101 (Feb.), 1953.

A left-to-right intracardiac shunt was demonstrated in 10 patients with pulmonary stenosis and a defect of the atrial or ventricular septum. Despite a significant degree of pulmonary stenosis, pulmonary artery pressure and flow were normal or increased. In the five patients with pulmonary stenosis and an interventricular septal defect, the systolic pressure in the right ventricle was not significantly different from the systolic pressure in a systemic artery. This observation may provide a differential point between pulmonary stenosis with a ventricular septal defect and pulmonary stenosis with atrial septal defect, for in the latter condition, the right ventricular systolic pressure is usually quite different from the systemic systolic pressure, being usually lower than, but sometimes equal to, or even greater than systemic systolic pressure.

SIMON

Denolin, H., Lequime, J., Wybauw, H., and Bollaert, A.: Interauricular Communication Associated with Pulmonary Hypertension and an Aberrant Pulmonary Vein. Acta cardiol. **8:** 64 (Fasc. 1), 1953.

The authors report the case of a 32 year old woman who was cyanotic from birth and developed progressive dyspnea at this age. A systolic murmur was heard in the third left intercostal space and a diastolic rumble was heard over the apex. The electrocardiogram showed pronounced right heart strain. X-ray films showed a huge pulmonary artery; in its right main branch, calcifications could be demonstrated by tomography. A cardiac catheter was passed first through an intra-atrial communication into the left atrium and into a left pulmonary vein, and then, into a right pulmonary vein, which drained into the right atrium. In both these vessels the blood was fully oxygenated despite the presence of marked pulmonary hypertension, pointing to an increase of pulmonary vascular resistance.

The authors discuss the meaning of the pulmonary hypertension and cyanosis observed in this case. The former appeared to be primary, but its mechanism, as in other types of congenital malformations, remained obscure. The cyanosis is explained by a veno-arterial shunt in the atria consequent to the marked increase of pulmonary vascular resistance.

PICK

Cosby, R. S., Griffith, G. C., Zinn, W. J., Levinson, D. C., Dimitroff, S. P., Oblath, R. W. and Jacobson, G.: Cardiac Catheterization in Interatrial Septal Defect. Am. J. Med. **14:** 4 (Jan.), 1953.

Evaluating their cardiac catheterization data in 10 patients with proven interatrial septal defects and in 7 presumptive cases, the authors found two classes of patients. The younger patients without cyanosis had high arterial oxygen saturations, high left atrial pressures, a marked rise of blood oxygen content between the vena cavae and the right atrium, full pulmonary vascular shadows, and frequently, a systolic thrill in the pulmonic area. Older patients and those with other defects or heart failure had a history of cyanosis, low arterial oxygen saturation, elevated right atrial pressures, little or no rise of oxygen content between the superior vena cava and right atrium, less prominent pulmonary vascular shadows, and an absence of pulmonic thrill. In making the diagnosis of interatrial septal defect, they emphasize the importance of passing the catheter through the defect into the left atrium. Otherwise errors may occur since a rise in the blood oxygen content of the right atrium in comparison with the oxygen content of the blood in the superior vena cava is not necessarily present in proven atrial septal defects. In such defects the pressure gradient between the auricles determines the direction of blood flow. The right-to-left shunt is the primary cause for cyanosis in atrial septal defects. When the shunt is from left to right, no cyanosis occurs. Although pulmonary vascular disease may contribute to the pulmonary resistance, it is not a significant factor in the production of cyanosis.

HARRIS

Metianu, C., Durand, M., Guillemot, R., and Heim de Balsac, R.: A New Case of Taussig-Bing Syndrome Diagnosed in Vivo and Verified Anatomically. Acta cardiol. **8:** 76 (Fasc. 1), 1953.

The authors report a case of ventricular septal defect with partial transposition of both aorta and pulmonary artery diagnosed clinically in a 6 year old girl and confirmed by autopsy. In this case two additional so far undescribed abnormalities were present, namely hypoplasia of the aortic arch distal to the origin of the left subclavian artery, and a large patent ductus arteriosus supplying the descending aorta.

X-ray examination showed marked prominence of the left middle segment and large pulsating pulmonary arteries. The electrocardiogram showed right heart strain. At cardiac catheterization pressure elevation of equal degree was found in the right ventricle and in the pulmonary artery. Gas analysis was not performed but a right-to-left shunt at ventricular levels was suggested by the ether test. Death ocurred in coma which developed suddenly, 48 hours after cardiac catheterization.

PICK

Loogen, F., Bayer, O., and Wolter, H. H.: Clinical and Physiologic Findings in Congenital Pulmonary Valvular Stenosis with and without Atrial Septal Defect. Ztschr. Kreislaufforsch. **42:** 115 (Feb.), 1953.

Clinical, hemodynamic, and angiocardiographic data are reported in 12 cases of congenital pulmonary stenosis, with and without an atrial communication. The main diagnostic criterion, common to both types, is a pressure gradient between right ventricle and pulmonary artery. Radiologically, there was invariably some degree of poststenotic dilatation of the main pulmonary artery. The electrocardiogram showed marked deviation to the right of the QRS vector, and large P waves in the limb leads. Phonocardiograms of the typical systolic murmur revealed a spindel contour between, and distinctly separated from, the two heart sounds.

In five cases of isolated pulmonary stenosis (with septa) there was normal arterial saturation, and in seven cases with auricular septal defect (trilogy of Fallot) there was distinct cyanosis. Catheterization in these cases revealed an intracardiac right-to-left shunt of 0.7 to 4.7 liter per minute. Calculations of the area of the stenosed pulmonary valve gave values varying between 0.2 and 1.2 sq. cm. Angiocardiography, which was performed in some of the cases showed a "late levogram" in cases of pure pulmonary stenosis, and an "early levogram" (simul-

taneous opacification of aorta and pulmonary artery) in cases of trilogy. The latter however is not diagnostic of this lesion and may be found in other cyanotic anomalies, with or without interatrial communication. The treatment of choice in valvular pulmonary stenosis is valvulotomy according to Brock, regardless of the presence or absence of an atrial septal defect.

PICK

Dammann, J. F., Jr., Berthrong, M., and Bing, R. J.: Reverse Ductus. A Presentation of the Syndrome of Patency of the Ductus Arteriosus with Pulmonary Hypertension and a Shunting of Blood Flow from Pulmonary Artery to Aorta. Bull. Johns' Hopkins Hosp. **92:** 128 (Feb.), 1953.

The authors describe four patients of ages between 20 and 36 years who suffered from the syndrome described in the title. Cyanosis beginning in childhood became progressively more severe with accompanying polycythemia. In one patient the left arm and the feet were markedly cyanotic in contrast to the right arm and face. In all, the oxygen content of the femoral arterial blood was significantly lower than that of the brachial artery blood. The second pulmonic sound was loud, there was electrocardiographic and fluoroscopic evidence of right ventricular hypertrophy, and pronounced pulmonary hypertension was demonstrated at cardiac catheterization. The characteristic machinery murmur of patent ductus was replaced by systolic and diastolic murmurs along the left sternal border. The diastolic murmur usually had characteristics suggesting pulmonic regurgitation. The main pulmonary artery was much dilated, but the peripheral lung fields were radiographically abnormally avascular. Two of the cases which came to postmortem examination revealed pulmonary vascular changes of occlusive nature. The authors state, however, that, "the pathogenesis of the pulmonary hypertension and of the pulmonary vascular lesions in these cases remains obscure." One of the patients, a 29 year old woman may have had an unusual predilection for vascular disease since both pulmonary arteries, the aorta, and the aortic valve were calcified and in the kidney, "a few glomerular arterioles revealed hyalinization of their walls."

MCKUSICK

Edwards, J. E.: Pathologic Features of Ebstein's Malformation of the Tricuspid Valve. Proc. Staff Meet., Mayo Clin. **28:** 89 (Feb.), 1953.

The author's experience with Ebstein's malformation of the tricuspid valve involves four cases, in one of which the detailed pathologic description is given; in the other three cases, the specimens were submitted by pathologists from other institutions. The oldest of the four patients concerned was a man 30 years of age at the time of death from an abscess of the pons. The second case was that of a 6 year old patient. The two youngest patients were each 2 months of age. In the case of the 30 year old man and in one of the two younger patients the tricuspid valve was deformed, and each also had an atrial septal defect. In the other young patient the deformity was of a milder degree in that the individual leaflets could be identified, but the septal and posterior leaflets were attached at levels lower than the annulus fibrosus. In addition, the tricuspid leaflets had nodular excrescencies of cellular fibrous tissue. It is impossible to say whether or not the tricuspid valve was competent in this case, although from the examination of the specimen it appeared probable that it had been incompetent. In this case there was also a ventricular septal defect.

As judged from the literature, hearts with Ebstein's malformation of the tricuspid valve have at times been considered to have incompetent tricuspid valves. This functional disturbance may result from inadequate length of existing leaflets to close the orifice. At other times perforations in the leaflets account for incompetence. The thin right ventricular wall which has frequently been observed in cases of Ebstein's malformation has been considered as an integral part of the malformation. The concept has to be entertained that the atrophic muscle seen in this condition may represent a secondary effect of the altered dynamics, rather than a primary muscular disturbance in association with the valvular deformity.

SIMON

Holman, E., Gerbode, F., and Purdy, A.: The Patent Ductus. J. Thoracic Surg. **25:** 111 (Feb.), 1953.

The authors reviewed their series of 75 patients with patent ductus arteriosus treated surgically. In eight of these division of the ductus was performed, while in the remainder multiple ligation in continuity was carried out. Only one death occurred. In two instances there was a recurrence, and in both, the operation had consisted of ligation either with one or several ligatures.

The authors expressed the opinion that a ductus arteriosus with or without symptoms should be closed by operation if it remains patent beyond the age of 5 years. Through such a procedure, the hazards of retarded physical development, cardiac decompensation, and bacterial endocarditis are avoided. Since a patent ductus is in effect an arteriovenous fistula within the heart, it places a great load on the right ventricle, thus eventually producing dilatation and congestive failure.

ABRAMSON

CONGESTIVE HEART FAILURE

Halmagyi, D., Felkai, B., Ivanyi, J., Zsoter, T., Tenyi, M., Szucx, Z.: The Role of the Nervous System in the Maintenance of Pulmonary Arterial

Hypertension in Heart Failure. Brit. Heart J. **15:** 15 (Jan.), 1953.

Sodium nitrite decreased pulmonary hypertension in nine individuals with congestive heart failure and abolished pulmonary hypertension produced by dihydroergotamine in 10 normal individuals. Tetraethylammonium bromide, in 10 individuals with cardiac failure and Dibenamine, in 8, reduced pulmonary pressure and resistance. These reactions are interpreted as evidence that pulmonary vasoconstriction can and does occur in heart failure.

Sleep likewise reduces pulmonary pressure. The release of pulmonary arteriolar constriction permits pulmonary pressure to be transmitted directly to the capillaries and thereby produces the syndrome of paroxysmal nocturnal dyspnea and pulmonary edema.

SOLOFF

CORONARY ARTERY DISEASE

Jaffe, H. L., Rosenfeld, M. H., Pobirs, F. W., and Stuppy, L. J.: Radioiodine in Treatment of Advanced Heart Disease. J.A.M.A. **151:** 716 (Feb. 28), 1953.

One hundred euthyroid patients with severe cardiac disease were treated with multiple small oral doses of radioactive iodine (I^{131}) and studied over a period of 24 months after therapy. Individual doses consisted of 6 mc. each of radioiodine in 20 cc. of distilled water. To produce myxedema levels or a relative hypothyroid state, 40 per cent of the patients needed only one course of 30 mc. of radioiodine, 54 per cent of the cases needed two courses or a total of 60 mc., and 6 per cent of the patients needed a total of three courses or 90 mc. for the same effect. Twenty-four patients died within the two-year period, but of these 33 per cent had had good symptomatic relief, 25 per cent had fair symptomatic relief, and only 42 per cent showed poor response prior to their deaths. In all cases death was due to the severe cardiac disease present prior to the beginning of treatment. However, if all 24 of these patients are scored as poor results, then the end result study showed 53 per cent good results, 20 per cent fair results, and 27 per cent poor results for this method of "medical thyroidectomy." Those favorably affected were relieved of the distressing cardiac symptoms of angina pectoris and congestive heart failure. No contraindications to this treatment have been found for properly selected patients. There was no evidence of bone marrow depression, radiation sickness, thyroiditis, or temporary hyperthyroidism. It was felt the average life expectancy of the entire group was not decreased and may actually have been increased. The success of this treatment requires the careful attention of the radiotherapist as well as careful management of the substitution thyroid medication by the internist.

KITCHELL

Smith, C.: Length of Survival after Myocardial Infarction. J.A.M.A. **151:** 167 (Jan. 17), 1953.

In 1942 the author (with Sauls and Bellew) reported on 100 consecutive patients with coronary thrombosis who were followed from 1930 to 1941. At the end of this 10-year period, there were 66 survivors from the original 100 patients. The present report deals with the situation at the end of the next 10 years (1952) when only 16 patients were alive and under the author's care. Sixty-nine were known to be dead and 15 had been lost in the follow-up. The youngest of the living patients was 51 years of age and the oldest 78. The author feels another 20 years may elapse before a final report on this series can be made. These 100 patients were followed from a minimum of 10 years to a maximum of 36 years, but it is felt that more long term follow-up studies will afford a better over-all prognostic picture for this disease.

KITCHELL

Hurlimann, A.: Resistance of Hearts with Coronary Occlusion to Anoxia. Am. J. Physiol. **172:** 437 (Feb.), 1953.

It required severe anoxia for more than 10 minutes with coronary ligation to produce acute heart failure. Less anoxia, gradually produced, was well tolerated after occlusion.

OPPENHEIMER

Levy, M. N., and Frankel, O. L.: Vasomotor Responses to Acute Coronary Occlusion in the Dog. Am. J. Physiol. **172:** 427 (Feb.), 1953.

Vasoconstriction was demonstrated in the hind legs of dogs following ligation of the anterior descending branch of the left coronary artery. Onset of fibrillation prevented the vasoconstriction in some cases, and in about 25 per cent of the cases there was no change in vasomotor tone. Blood pressure fell after the occlusion. These effects were not due to ischemic reflexes from the ischemic myocardium.

OPPENHEIMER

Bailey, C. P., Truex, R. C., Angulo, A. W., Geckeler, G. D., Likoff, W., Antonius, N., and Neptune, W. B.: The anatomic (Histologic) Basis and Efficient Clinical Surgical Technique for the Restoration of the Coronary Circulation. J. Thoracic Surg. **25:** 143 (Feb.), 1953.

The authors present anatomic evidence supporting the view that retrograde flow into the myocardial capillary bed can be produced by shunting arterial blood into the coronary sinus, provided the orifice of the latter in the right auricle is narrowed. They admit the existence of communications between the superficial cardiac and the deeper myocardial veins, with drainage of these into the cardiac chambers, but they believe that shunting of the arterial blood through such channels affords a valuable

safety mechanism which would regulate the retrograde flow.

On the basis of anatomic investigations, the authors have found that arterialization of the coronary sinus with the Beck procedure permits arterial blood to enter the capillary bed of the left heart by retrograde flow through tributaries of the coronary sinus. Branches of the latter also establish epicardial anastomoses with the small cardiac and anterior cardiac veins of the right ventricle, thus permitting it to receive arterial blood. In time a progressive and great dilatation of the normally minute existing intercoronary communications is brought about.

Because of such possibilities and because of the subjective improvement in patients who have undergone both stages of a Beck procedure, the authors believe that this operation should continue to be investigated as a means of therapy in coronary arteriosclerosis.

ABRAMSON

ELECTROCARDIOGRAPHY

Reynolds, G.: The Electrocardiogram during Angiocardiography. Brit. Heart J. **15:** 74 (Jan.), 1953.

An analysis is made of 75 electrocardiograms taken during angiocardiography on 73 patients with cyanotic congenital heart disease. Sixty per cent of the electrocardiograms showed changes thought to be significant. They occurred more frequently in the younger age group, in the more disabled, and in those under an anesthetic. Attempts were made to attribute the changes to (1) Diodone, (2) anesthetic, or (3) causes unrelated to the procedure. Arrhythmias, mostly premature contractions, occurred in about 25 per cent and appeared to be due to the anesthetic. Conduction defects, mostly prolonged P-R intervals, had a similar incidence and appeared to be due to Diodone. S-T segment alterations were due to all three factors. A drop in blood pressure was almost constant after the injection and at times followed by collapse.

The author suggests that angiocardiography should not be done in those with changes in conduction or S-T segment not due to quickly rectified anoxia.

SOLOFF

Henderson, C. B.: Potassium and the Cardiographic Changes in Diabetic Acidosis. Brit. Heart J. **15:** 87 (Jan.), 1953.

Fifty-two electrocardiograms and blood for determination of potassium were taken on 10 individuals treated for diabetic acidosis. In half, there was no correlation between the blood potassium and the electrocardiographic pattern. For this reason, the author considers tissue potassium as the important factor. A pattern is described of high T waves in the medial and low T waves in the lateral precordial leads. Arrhythmias and changes in the P and QRS complexes were found frequently.

SOLOFF

Gross, D.: On the Comparative Measurement of the Q-T Interval in Leads 1 and 3 in Cases with a Negative T Wave. Prensa méd. argent. **11:** 1:8 (Jan. 16), 1953.

The author studied the duration of the Q-T interval in 150 cases with a negative T wave in either lead 1 or lead 3. The Q-T interval was measured in both leads and a $Q\text{-}T_1/Q\text{-}T_3$ ratio was calculated.

The Q-T interval in lead III with a negative T was found shorter in normal subjects and larger in posterior myocardial infarction than in the positive T of the same cases. The Q-T interval in lead I with a negative T was found shorter than in lead III in all three groups of cardiac patients which were investigated.

The Q-T interval of the lead with inverted T, however, may be as long as that of the lead with normal T, both in normal subjects and in cardiac patients. As the cause of a short Q-T interval in only one lead is unknown, the interpretation is purely hypothetic.

LUISADA

Arcuri, R. A., Newman, W., and Burstein, C. C.: Electrocardiographic Studies during Endotracheal Intubation. V. Effects during General Anesthesia and Hexylcaine Hydrochloride Topical Spray. Anesthesiology **14:** 46 (Jan.), 1953.

Previous studies have demonstrated that the high incidence of electrocardiographic disturbances occurring during endotracheal intubation in the course of general anesthesia can be significantly reduced by the prior administration intravenously of procaine, diethylaminoethanol, or procaine amide. Topical anesthesia of the pharynx and larynx with cocaine increased the incidence of arrhythmias, especially ventricular premature beats. A new local anesthetic agent, "cyclaine" (5 cc. of a 5 per cent aqueous solution), was investigated in 50 patients in whom endotracheal intubation was to be performed. Electrocardiograms were recorded (1) during light surgical anesthesia, (2) during exposure of the glottis and spraying, (3) at the time of intubation, and (4) three to five minutes after intubation. The general anesthesia employed was cyclopropane-ether in 20 patients, cyclopropane alone in 11, and various other combinations of agents in the remaining 19. It was found that cyclaine was an efficient topical agent for the larynx, had a low order of toxicity, and also showed an antiarrhythmic effect

similar to procaine. With this agent the over-all incidence of arrhythmias was 30 per cent and the actual incidence during intubation was 14 per cent. This incidence compares favorably with that observed with procaine, diethylaminoethanol, procaine amide, and with the incidence of arrhythmias of 60 per cent when no antiarrhythmic agent is employed.

SAGALL

Beck, H. D., and Ramer, W.: Electrocardiographic Findings with Dibenamine Therapy. Ztschr. Kreislaufforsch. **42:** 62 (Jan.), 1953.

Repeated intravenous infusions of Dibenamine (5 mg. per kilogram in 1000 cc. physiologic saline solution) produced the following alterations of the electrocardiogram. In 18 out of 22 patients there was a definite increase of the heart rate. In eight patients the T wave became smaller in the supine position and more upright in standing position. In eight patients the development of supraventricular and ventricular premature beats and of second degree A-V block was observed. With repeated injections the susceptibility to alterations of the rate and of the contour of the T wave diminished, but the tendency to ectopic impulse formation increased. The authors conclude that sympatholytic agents like Dibenamine should be used with caution, especially in cases with organic heart disease.

PICK

Di Giuseppe, F.: The Ballistocardiogram in Acquired Valvular Defects. Acta cardiol. **8:** 22, 1953.

The ballistocardiograms of 31 cases of rheumatic valvular disease were studied. Thirteen were cases of pure mitral stenosis, three had mitral stenosis and insufficiency, six had pure mitral insufficiency, and nine had aortic insufficiency or mitral plus aortic insufficiency.

The typical changes of the ballistocardiogram in cases of mitral stenosis were: (a) decreased amplitude of the HI waves without change of the J-K segment, which is attributed to decrease of systolic discharge, and (b) increased amplitude of the L wave, which is attributed to increased blood flow into the ventricles during rapid filling.

An increase of the J-K segment was observed in cases of aortic insufficiency.

LUISADA

Germer, W. D., Zeh, E., and Fischer, L.: The Electrocardiogram in Endocarditis Lenta. Arch. Kreislaufforsch. **19:** 69 (Feb.), 1953.

In 100 cases of subacute bacterial endocarditis, electrocardiographic findings were correlated with the size of the heart, the presence or absence of heart failure, the activity of the process, and the degree of dysproteinemia. For comparison the same study was made on 64 cases of rheumatic heart disease with aortic involvement.

A single electrocardiogram can not be evaluated with respect to the investigated factors. Serial tracings, however, correlated well with the clinical course of the patients. Thus the development of bundle branch block or of low voltage was seen only in cases with unfavorable outcome, while improvement of other electrocardiographic alterations goes along with clinical recovery.

Comparison of electrocardiographic alterations occurring in subacute bacterial endocarditis with those observed in rheumatic heart disease revealed certain differences which might be of diagnostic value. Thus, in contrast to rheumatic heart disease, the development of ST-T alterations is not related to the presence of cardiac hypertrophy and/or dilatation. Hence, in questionable cases, abnormalities of ST-T in the absence of cardiomegaly support the diagnosis of subacute endocarditis. Abnormalities in right-sided chest leads were twice as frequent in subacute bacterial endocarditis as in other types of valvular lesions. In no case was there unusually high voltage, which is present in about 8 per cent of uncomplicated rheumatic heart disease.

PICK

Friese, G., and Baer, Ch.: The Relationship of the Amplitude of the P wave to the Heart Rate in Normal Electrocardiograms. Arch. Kreislaufforsch. **19:** 82 (Feb.), 1953.

In electrocardiograms of normal persons the author determined the amplitude and area of the P waves at various heart rates, and correlated the angle of P with that of QRS and with the area of P.

The heart rate influences only indirectly the size of the P wave. The latter changes because of an altered position of the heart at various rates as is evidenced by the simultaneous occurrence of alterations of the QRS vector. Both the direction of the P vector and the area covered by the P wave depend on rotation of the heart along its longitudinal or sagittal axes.

PICK

Rocher, P.: Electrocardiographic Aspects of Diffuse Pulmonary Sclero-emphysema. Arch. mal. coeur **46:** 63 (Jan.), 1953.

The author analyzed 12-lead electrocardiograms of 21 cases with pulmonary emphysema and impairment of breathing capacity. The tracings could be divided into four types. Type I, which was normal in every respect, was found only exceptionally.

Most commonly, a second type was seen with low voltage in the frontal plane and a distinct S wave in leads I to III, the QRS axis being horizontal. In some cases the QRS-T angle was larger than 60 degrees which is ascribed to concomitant coronary disease rather than to left heart strain. The third type was characterized by normal or high voltage with the QRS axis at + 70 degrees, and the presence of distinct Q waves in leads II and III. Frequently there also was a notching of the terminal basal portion of QRS best seen in leads II, III, and aV_F. The fourth type showed evidence of heart strain, mainly evident on the P waves which revealed right axis deviation. This, however, is not diagnostic of pulmonary emphysema. Signs of right ventricular strain were found only exceptionally.

PICK

Lian, C., Minot, G., Hebert, N., and Rager, N.: The Chronologic Relationship of Mechanical and Electrical Events of the Heart. Arch. mal. coeur **46:** 39 (Jan.), 1953.

The authors recorded in dogs and man synchronously the electrocardiogram, the apical electrokymogram, the heart sounds, and the right ventricular pressure. The following new observations were made.

The first heart sound starts 0.02 to 0.04 second *before* the brusque elevation of the intraventricular pressure. To explain this curious phenomenon it is assumed that the sudden transformation of the ovoid mitral ring to a slit-like opening at the very beginning of the ventricular contraction produces an acoustic phenomenon, which precedes that effected by the actual closure of valvular leaflets.

A second, hypothetic deduction, based on the obtained data refers to the theory of the electrocardiographic deflections. Since the beginning of QRS precedes by about 0.03 second the onset of mechanical systole, it must be a phenomenon which is independent of mechanical alterations of the heart and represents the moment of electric activation of the heart. During the contraction of the heart, this deflection returns to, and remains at the isoelectric level. The final event, the T wave, coincides with the ejection of blood from the ventricles, since the second heart sound occurs only at the end of the T wave. It seems probable, therefore, that the mechanical event of ventricular ejection is in some direct or indirect way related to the electrical phenomenon producing the T wave of the electrocardiogram. The same relationship of mechanical and electrical events seems to account for the formation of the P wave.

PICK

HYPERTENSION

Mason, A. A., and Pelmore, J. F.: Combined Use of Hexamethonium Bromide and Procaine Amide in Controlled Hypertension. Brit. Med. J. **1:** 250 (Jan. 31), 1953.

The authors demonstrate synergism of the two agents mentioned as far as hypotensive action is concerned and describe experiences with use of the combination for producing controlled hypotension for surgical procedures. Procaine amide prevented development of the usual tachycardia with hexamethonium.

McKUSICK

Moyer, J. H., Miller, S. I., Tashnek, A. B., Snyder, H., and Bowman, R. O.: Malignant Hypertension and Hypertensive Encephalopathy. Cerebral Hemodynamic Studies and Therapeutic Response to Continuous Infusion of Intravenous Veriloid. Am. J. Med. **14:** 175 (Feb.), 1953.

Continuous infusions of intravenous veriloid lowered significantly the blood pressure in 27 patients with severe hypertension who exhibited various degrees of encephalopathy. Continuous infusions for prolonged periods of time improved the encephalopathic manifestations in 13 of 17 patients. In four instances the drug was discontinued within 24 hours because of vomiting or severe hiccoughing. Most of the patients exhibited minor side reactions. The cerebral blood flow studies showed a marked reduction in cerebrovascular resistance which paralleled the reduction in systemic blood pressure, thus indicating that cerebrovascular dilatation is physiologically possible. Cerebral blood flow was thus maintained. Cerebral blood flow was not altered significantly. These observations are another indication that the regulation of cerebral blood flow is probably not under the control of the autonomic nervous system. Hypertensive encephalopathy of relatively short duration is not associated with depressed cerebral blood flow. The changes in cerebral function appear related to the high arterial pressure which is probably transmitted to the postarteriolar capillaries, resulting in increased cerebral tissue pressure and altered cellular function.

HARRIS

Dole, V. P., Dahl, L. K., Schwartz, I. L., Cotzias, G. C., Thaysen, J. H., and Harris, C.: Dietary Treatment of Hypertension. III. The Effect of Protein on Appetite and Weight. J. Clin. Investigation **32:** 185 (Feb.), 1953.

Prolonged detailed metabolic studies on six patients with hypertension revealed the following findings: changes in the appetite and weight were produced consistently by changes in the ration of protein; a decrease in protein intake resulted in reduction in caloric intake and was due to a variation in the quantity of nonprotein constituents. The reduction in dietary protein was followed invariably

by reduction in body weight and vice versa. The variations in weight were not due to changes in hydration. The feeding of protein must have stimulated a consumption of calories in excess of expenditure. Patients remained hypertensive during control periods in which the diet was supplemented with 10 Gm. of salt a day but responded to omission of salt with a decline in pressure. Statistical analysis confirmed the impression that the quantitative reduction of pressure was unrelated to the state of protein metabolism. The data indicate that restriction of dietary sodium may be expected to reduce the systolic and diastolic pressures by 12 ± 7.4 per cent.

The authors discuss the effect of low protein diets on weight loss without hunger or weakness and suggest the possibility of similar mechanisms in successful treatment of obesity.

WAIFE

Goldman, R., and Frierson, H. R.: Effect of Veriloid Upon Renal Function when Administered in Hypotensive Doses to Patients with Arterial Hypertension. Am. J. Med. **14:** 168 (Feb.), 1953.

Veriloid, administered intravenously to 17 patients, consistently produced a stable hypotensive effect for periods of 4 to 10 hours. All patients responded. The average fall in the systolic blood pressure was 28 per cent; the average fall in the diastolic pressure was 24 per cent. A concomitant 10 per cent slowing in the pulse rate was also observed. No serious toxic side effects were observed in this group other than nausea and vomiting in slightly more than one-half of the patients. In almost all individuals there was a moderate reduction in the glomerular filtration rate, an increase or maintenance of the renal plasma flow, and a resultant reduction in the filtration fraction. A profound antidiuresis observed during the first four hours tended to be reduced during the subsequent period, but was not completely eliminated at the end of 10 hours. The renal hemodynamic changes seem to indicate that the renal arterioles participate in the general reduction in arteriolar resistance produced in response to the administration of veriloid. A small group of patients, all of whom had initial systolic pressures above 185 mm. Hg, exhibited a marked fall in the glomerular filtration rate and renal plasma flow, and a moderate increase in the filtration fraction after administration of the drug. It is believed that these patients actively responded to the reduction in systemic blood pressure by a further renal hypertensive response, that is, further efferent arteriolar constriction as indicated by an increased filtration fraction. These patients also failed to show reversal of the antidiuretic effect of the drug even after 10 hours.

Veriloid is a promising antihypertensive drug which generally, but not invariably, results in the return of renal hemodynamic mechanisms toward normal. This is accompanied by a moderate reduction in filtration rate which should not seriously increase the degree of uremia. In a few patients the reduction of function and the profound antidiuresis may be detrimental if continued for a prolonged period.

HARRIS

Morris, N.: Hexamethonium Compounds in the Treatment of Pre-eclampsia and Essential Hypertension During Pregnancy. Lancet **1:** 322 (Feb. 14), 1953.

Whether significant benefit accrued to any of 10 mothers to whom Hexamethonium was administered was uncertain. Oral therapy was advised against because of the possible detriment to the fetus from excessive hypotension. Resistance to the hypotensive action of the agent frequently developed within a few days and at a time when "the drug still caused the same degree of pupillary paralysis." The progress of labor was unaffected. There were strong suspicions that serious ill-effects to the fetus resulted. The author demonstrated an accumulation of Hexamethonium in the amniotic fluid to levels considerably exceeding the level in mother's plasma. (Evidence from animals suggests the urine of the fetus may be the source of this accumulated drug since the phenomenon does not occur if the umbilical cord is ligated.) Two infants out of 10 in this group died of paralytic ileus. One passed no meconium for 20 hours. One died 72 hours after birth from widespread purulent bronchopneumonia. The author suggests that swallowing of amniotic fluid may be responsible for the intestinal complications, whereas its aspiration with drying of bronchial secretions may favor respiratory infections.

MCKUSICK

Allen, E. V.: A Survey of Opinion About Sympathectomy for Essential Hypertension. Proc. Staff. Meet., Mayo Clin. **27:** 495 (Nov.), 1952.

This study presents briefly many viewpoints and opinions. The many aspects about which there is disagreement can be resolved only by a careful plan of case matching. It seems unlikely that this will be accomplished in the future, however desirable it may be. Many patients are benefited by sympathectomy, but unfortunately there is no method or methods by which proper selection can be made in order that only those patients will be operated on who will be benefited. It is agreed that azotemia is a contraindication to sympathectomy and it seems likely that patients with other advanced complications of hypertension respond less well than those who have "compensated" hypertension. Physicians should

not carry on medical treatment which has little or no benefit until the "golden period" in which sympathectomy might benefit, has passed. It is probable that no additional technics of sympathectomy will produce better results than those currently in use. It is logical to believe that if the problem of essential hypertension is solved, it will be solved by medical measures. Until that time, patients who have a reasonable prospect of benefiting from sympathectomy should not be denied this surgical procedure, if a short period of adequate medical treatment does not cause satisfactory reduction of blood pressure.

SIMON

Bakke, J. L., and Williams, R. H.: Treatment of Essential Hypertension with B-Alkylamines, Especially Dibenzyline. Am. J. Med. **14:** 141 (Feb.), 1953.

The authors carried on clinical studies with six congeners of Dibenamine during the past five years on 103 patients. Twelve of 24 patients who received Dibenzyline intravenously in doses of 7 to 150 mg. had a fall in blood pressure with associated adrenergic blockade and occasional untoward effects including shock, stupor, and coma. Postural hypotension persisted for one to four days after the injection. Eighty-five patients received 128 courses of oral therapy. Of the six compounds only Dibenzyline was effective. Thirteen per cent showed a marked decrease in blood pressure and another 20 per cent, a definite though less pronounced effect. Sixty-seven per cent failed to respond. Only 13 per cent reported symptomatic benefit from Dibenzyline. Eighty-seven per cent reported nasal congestion, 67 per cent reported dizziness, especially upon standing, 54 per cent reported indigestion, anorexia, nausea and occasional vomiting, 31 per cent reported fatigue and weakness, 8 per cent reported epitaxis. Others reported blurred vision, palpitations, and shortness of breath. Undesirable effects diminished with continued therapy, but hypotensogenic effects also diminished. The authors conclude that Dibenzyline administered orally is of limited value in the treatment of essential hypertension. Further clinical investigation of Dibenzyline, especially in combination with other hypotensogenic agents and procedures, would seem to be indicated.

HARRIS

Riven, S. S., Popcock, D. G., Kory, R. C., Roehm, D. C., Anderson, R. S., and Meneely, G. R.: The Control of Hypertension with l-Hydrazinophthalazine (Apresoline). Am. J. Med. **14:** 160 (Feb.), 1953.

In their series of 65 hypertensive patients treated with l-hydrazinophthalazine the authors discovered that patients with essential hypertension or malignant hypertension responded favorably to the administration of this drug, but that patients with hypertension of the "renal" type showed only an insignificant response. Postsympathectomy patients with persistent hypertension had variable responses and judgment as to the value of the drug must be delayed until more cases are studied. Undesirable side effects caused 10 patients to discontinue the drug. Although only intermediate in depressor ability, l-hydrazinophthalazine proved capable of producing greater over-all improvement in ballistocardiographic contours than other drugs tested.

HARRIS

Brodsky, W. A., and Graubarth, H. N.: Excretion of Water and Electrolytes in Patients with Essential Hypertension. J. Lab. & Clin. Med. **41:** 43 (Jan.), 1953.

Six patients with uncomplicated hypertensive disease, under standard conditions of hydropenia were tested by the technic of osmotic loading. Mannitol as the loading solute was given in amounts sufficient to add 20 milliosmoles per liter of distribution volume.

The urinary flow was higher and the osmotic activity lower than normal under both "resting" or preliminary and loading conditions. Subjects were excreting urine at rates of 0.33 to 1.70 ml. per minute and submaximal osmolarities of 557 to 806 milliosmoles per liter. Following loading the flow rose to 10 to 14 ml. per minute and osmolarity fell to 375 to 400. For a given solute load, patients with hypertension excreted urine at a rate of about 1 and 15 times that of normal subjects.

Minute losses of sodium and chloride during diuresis were 2 to 2.5 times greater than normal, reaching values of 1.8 and 1.4 mEq. per minute, respectively. The percentage composition of urinary solutes differed from that of normal subjects under identical loading conditions. While sodium and chloride comprised higher, mannitol and urea comprised lower than normal proportions of the total urinary solutes. The calculated values of ideal osmotic work were less than one-half those of normal subjects.

Clearances of mannitol, at 63.5 ml. per minute, were 25 per cent below normal, while those of para-aminohippurate, at 312 ml., were 50 per cent of normal. The filtration fractions were elevated.

It was postulated that defective concentrating ability implied distal, and distorted composition of urinary solutes, proximal tubular dysfunction.

The data indicated that under certain conditions salt-losing may be a common concomitant finding in apparently uncomplicated hypertensive disease.

MINTZ

PATHOLOGIC PHYSIOLOGY

Yu, P. M. G., Lovejoy, F. W., Jr., Joos, H. A., Nye, R. E., Jr., and McCann, W. S.: Studies of Pulmonary Hypertension. I. Pulmonary Circulatory Dynamics in Patients with Pulmonary Emphy-

sema at Rest. J. Clin. Investigation. **32:** 130 (Feb.), 1953.

Eighteen patients with pulmonary emphysema ere studied by the cardiac catheterization technic. number of detailed physiologic studies revealed at the mean pulmonary artery pressure exceeded 5 mm. Hg in 14 of the 18 patients. In general the egree of hypertension varied directly with severity hypercapnia, emphysema, and anoxia, and inersely with the vital capacity. In none of the subcts did the "pulmonary capillary" pressure exceed 2 mm. Hg, the upper limit in normal subjects. he oxygen saturation of arterial blood varied inrsely with the mean pulmonary artery pressure ut did not parallel the other determinants. Arterial arbon dioxide tension correlated closely with the ean artery pressure. The authors call attention to he probable importance of carbon dioxide retention n increasing pulmonary vascular resistance and levating the pulmonary artery pressure.

WAIFE

Richards, B. G. B., Whitfield, A. G. W., Arnott, W. M., and Waterhouse, J. A. H.: The Lung Volume in Hyperkinetic States. Brit. Heart J. **15:** 83 (Jan.), 1953.

The vital capacity, the complemental and reserve air, the functional residual air, and the residual air, were measured before and after successful treatment in 10 individuals with hyperthyroidism and 9 with anemia.

In both diseases, the vital capacity and complemental air are diminished and the functional residual air and residual air are increased, and in anemic subjects these changes are correlated with the severity of the anemia.

The mechanism for these changes is not understood.

SOLOFF

ROENTGENOLOGY

Miller, G., Lowenthal, M., Krause, S., and Rosenblum, P.: A Saccular Outpouching of the Right Ventricle in a Child Visualized by Angiocardiography. Am. J. Roentgenol. **69:** 69 (Jan.), 1953.

A case is reported of a 12 year old boy in whom on angiocardiographic examination a small saccular outpouching was observed extending out from the apex of the right ventricle. This was thought to be either a congenital diverticulum or a small saccular ventricular aneurysm. The boy was completely asymptomatic, and presented no significant signs of heart disease, except for questionable cardiac enlargement. The findings during cardiac catheterization were normal.

SCHWEDEL

Moniz de Bettencourt, J., Saldanha, A., and Barreta Frageso, J. C.: Tomography of the Pulmonary Veins in Mitral Disease. Arch. mal. coeur **45:** 1074 (Dec.), 1952.

In 40 cases of mitral valvular lesions the pulmonary veins could be vizualized with the help of tomography. This was done in addition to conventional clinical, radiologic and electrocardiographic examinations. In about half of the cases, pulmonary arterial and capillary pressure were determined by cardiac catheterization.

The pulmonary veins seen clearly in the tomograms were classified into three groups according to their size. In general, no marked enlargement was found. There appears to be a relationship between the dimension of the pulmonary veins on one hand and the heart rhythm, size of the left auricle and pulmonary capillary pressure on the other. Large pulmonary veins were usually found in cases with sinus rhythm, a relatively small left auricle and normal pulmonary capillary pressure, whereas small veins were associated with large, fibrillating left auricles and increased papillary pressure. Considerable left auricular enlargement tends to displace the pulmonary veins so that they may become invisible.

These observations are discussed and explained from the viewpoint of the pathophysiology of mitral valvular lesions. The authors believe that a possible factor involved is an alteration of the venous tone.

PICK

Segers, M., and Brombart, M.: The Esophagus in Cardiology. Acta cardiol. Suppl. 5, 1952.

This monographic issue is devoted to x-ray studies of the esophagus for diagnosis of cardiovascular disease.

Following an introduction by Professor Laubry, the normal structure of the esophagus and the roentgenologic technic are explained in detail. The study of the left atrium is particularly stressed for its interest in rheumatic heart disease. Two chapters are devoted to the study of the left ventricle and of the right heart. The aorta is studied in detail. Then, the congenital malformations are described including the right aortic arch, the double aortic arch, the right subclavian arising from the left side, coarctation of the aorta, and the patency of the ductus. Last, dysphagia is studied in relationship with cardio-aortic disturbances. This chapter discusses the dilatation of cardiac chambers, the aneurysms of the aorta, hiatus hernia, deviation of the esophagus, and the congenital malformations of the aorta.

This issue is richly illustrated by 135 sketches and photographs and contains a complete bibliography.

LUISADA

Silver, C. P.: The Radiological Pattern of Injected Pulmonary and Bronchial Arteries. Brit. J. Radiol. **25:** 617 (Dec.), 1952.

The pulmonary arteries were injected with radiopaque suspensions in 27 lungs or lobes and the

bronchial arteries in both lungs in seven subjects, and the specimens subsequently radiographed.

When the pulmonary arteries were injected, both arterioles and larger vessels could be readily visualized. In normal lungs no anastomosis between pulmonary and bronchial arteries could be demonstrated. In areas of pulmonary film and in lobular collapse the main pulmonary arteries persisted while the lesser branches were narrowed, crowded together and diminished in number. In bronchiectasis and in instances of long-standing pulmonary infection the bronchial arteries were enlarged, tortuous, anastomosed with each other and also with the smaller pulmonary arteries.

SCHWEDEL

SURGERY IN HEART AND VASCULAR SYSTEM

Hahn, R. S., Kim, M., and Beck, C. S.: Revascularization of the Heart. Observations on the Circulation Following Arterialization of the Coronary Sinus. Am. Heart J. **44:** 772 (Nov.), 1952.

The authors discuss their observation on the circulation following arterialization of the coronary sinus. They show that such arterialization will significantly lower the mortality of dogs, even when the descending ramus of the left coronary artery is ligated, as compared with normal dogs and those animals whose graft is occluded by a thrombosis. The preparation for the experiment is as follows: a segment of jugular vein is placed between the coronary sinus and the aorta of the dog and several weeks later the coronary sinus is occluded to 2 to 3 mm. at the ostium of the sinus in the right auricle. At the second operation the right coronary artery is totally occluded at its origin. At a third operation several weeks later, the common left coronary artery is dissected out with the circumflex ramus. The circumflex ramus is ligated at its origin and then cut distal to the ligature. The distal end is cannulated with a piece of polyethylene tubing.

With this preparation, the arterial pressure is consistently higher with an open graft as compared with the figures obtained with a closed graft, and the pressure with an open graft remains on a higher level regardless of the degree of coronary artery inflow occlusion. The pressures with the graft closed off progressively fall as the amount of coronary artery occlusion is increased. The backflow of blood measured in cubic centimeters per minute is uniformly greater with the graft open and increases as arterial inflow is reduced. The oxygen content of the retrograde blood is greater with the graft closed than with it open. The authors attribute this reduction in oxygen content of the retrograde blood when the graft is open to the fact that it is aortic blood which has traversed a capillary bed before it reaches the circumflex ramus, while the red blood which is seen when the graft is shut off must come by way of intercoronary arteries without first traversing a capillary bed.

Other observations include evidence that the arterial and venous system may be in direct communication in the heart of the human and dog without the interposition of a capillary bed.

RINZLER

Falconer, M. A.: The Future of Surgery in the Treatment of Spontaneous Cerebral Haemorrhage. Lancet **2:** 945 (Nov. 15), 1952.

The author considers that intracranial aneurysms "are really all acquired lesions which develop as a result of degenerative processes affecting the arterial wall at a site already weakened by a congenital deficiency of the muscular coat." Aneurysms of the posterior communicating artery may bleed into the subdural space producing subdural hematoma. The author deems severe hypertension with advanced vascular disease a contraindication to cerebral angiography because of dangers of spasm and thrombosis. He does bilateral carotid angiograms early, usually within a week of the onset of symptoms. Extra- and intracranial procedures for treatment of aneurysms are reviewed. Representative cases illustrating the occasional beneficial effects of evacuation of intracerebral hematomas are presented.

MCKUSICK

Cooley, D. A., and Chapman, D. W.: Mitral Commissurotomy during Pregnancy. J. A. M. A. **150:** 113 (Nov. 15), 1952.

The prognosis in heart disease complicated by pregnancy is based primarily on the threat or the presence of cardiac decompensation. By means of rigid cardiac regimens including digitalis, salt-poor diet and strict bed rest during the critical period of pregnancy, the mortality rate even in poor risk patients has been significantly reduced. Seventy-five per cent of the cardiac lesions that occur in pregnant women involve the mitral valve alone, usually with mitral stenosis, with or without mitral insufficiency. Not infrequently a patient is encountered with pure mitral stenosis for whom no one concerned is content with expectant conservatism and its associated risk to the mother. In such patients the desirable solution to the problem is mitral commissurotomy if such a procedure is feasible during pregnancy. The authors report two such cases. In one, a 28 year old primipara with mitral stenosis, commissurotomy was well tolerated during the fourth month of pregnancy and normal delivery occurred at the date of confinement. In the second case, a 23 year old primigravida in the thirty-sixth week of pregnancy, commissurotomy was performed and sixty-two hours afterwards delivery was accomplished by low forceps. Mother and infant were discharged from the hospital five days later.

KITCHELL

Bailey, J. E.: Repair of Funnel Chest Using Substernal Osteoperiosteal Rib Graft Strut. J. A. M. A. **150:** 1203 (Nov. 22), 1952.

In 1938 Alton Ochsner and Michael DeBakey described 32 operative technics used since 1911 to correct funnel chest deformity (commonly known as pectus excavatum). The author discusses the three reasons for surgery in these cases: (1) cardiac symptoms, (2) respiratory symptoms, (3) psychologic complaints. A new technic is proposed for repair of this condition using a substernal osteoperiosteal rib graft as a strut in the older age group. The case of a 13 year old girl, operated on in February 1948, and followed for four years after operation, is discussed. Evidence is shown that an osteoperiosteal bone graft (rib) used to bridge a wide gap remained completely fused and functioning after four years, with no structural change. The author suggests that this type of graft in other orthopedic or plastic procedures might be useful for bridging a gap. He also states that a comparison of results using rib bones from a bank with and without attached periosteum would be interesting.

KITCHELL

Gross, R. E., Watkins, E., Jr., Pomeranz, A. A., and Goldsmith, E. I.: A Method for Surgical Closure of Interauricular Septal Defects. Surg., Gynec. & Obst. **96:** 1 (Jan.), 1953.

Since an interauricular septal defect reduces life expectancy, the authors attempted to devise a procedure which could be utilized to obliterate the opening. After considerable trial and error, they constructed a rubber well which was attached to the wall of the right auricle with a number of interrupted stiches. Then this portion of the auricle was penetrated so as to allow the examining finger to enter the cavity.

The method was tried out on 68 dogs with artificially made septal defects. In some the opening was closed using plastic buttons, onlay of discs, or sheets of plastic materials, while in others, suture closure was attempted. The animals were sacrificed at varying periods of time up to six months after operation. In 60 dogs, complete closure was noted at autopsy. It was concluded that success in the obliteration of the septal defect was closely related to the extent of the operator's experience and manual dexterity.

Because of the satisfactory results in dogs, the authors felt justified in attempting the procedure in seven human subjects. Since the auricular pressures in man with cardiac anomalies was believed to be higher than those in dogs, a large rubber well was constructed. In three patients double disc buttons were used to occlude the defect and in each case death occurred. In three other subjects a sheet of nylon or polyethylene was substituted. Two of these survived the operation while the third died. In the case of the last patient, primary suture was attempted and a successful result occurred.

ABRAMSON

Lord, J. W. Jr., von Wedel, J., Stone, W., Neuman, G., Hinton, J. W., and Moran, R. E.: Cardiac Revascularization by Means of a Skin Flap Transplant. An Experimental Study. 4th Inter-American Congress of Cardiology. Rev. argent. cardiol. **19:** 300 (Sept.–Oct.), 1952.

Animal experiments were carried out in order to create a new blood supply to the myocardium by grafting a cutaneous flap. The surgical procedure of grafting a pediculated skin flap over the myocardium of the left or right ventricle was well tolerated and there were no surgical fatalities. Cardiac function remained normal in all animals during the postoperative period.

The authors further injected a 20 per cent aqueous solution of bismuth oxychloride, whose particles are too large for passing through the capillaries. They demonstrated an ample web of macroscopic anastomosis between the arteries of the skin flap and the coronary vessels.

All animals which had such skin flaps for one month or more survived the ligation of the anterior descending branch of the left coronary artery.

LUISADA

Nabatoff, R. A., Touroff, A. S. W., Gross, M., and Brahms, S.: The Use of Maximal Size Vena Cava Autografts to Bridge Experimental Aortic Defects in Dogs. I. Studies of Collateral Circulation and Venous Pressure Following Resection of Long Segments of Inferior Vena Cava. Surg., Gynec. & Obst. **96:** 87 (Jan.), 1953.

The authors studied the effect of utilizing inferior vena cava autografts to replace experimentally produced aortic defects in 20 dogs. Fourteen animals survived the operation. In this group the venous pressures in the lower extremities rose rapidly postoperatively, but by 24 to 48 hours it had fallen almost to normal. Serial venograms demonstrated the rapid development of collateral vessels.

It was concluded that segments of inferior vena cava between the renal and iliac veins could be excised with impunity and used to bridge experimental aortic defects in dogs.

ABRAMSON

McGoon, D. C., and Henly, W. S.: The Significance of Auricular Fibrillation and Auricular Thrombosis in Mitral Valve Surgery. Bull. Johns Hopkins Hosp. **91:** 419 (Dec.), 1952.

The authors found that auricular fibrillation had occurred in approximately half of a group of 89 autopsied cases of mitral stenosis. In a group of 58 patients, auricular fibrillation had occurred in 38 per cent before mitral commissurotomy was per-

formed. Most of the patients with auricular thrombi had had auricular fibrillation; about half the cases of fibrillation were found to have auricular thrombi at autopsy or operation. In 13.5 per cent of the patients who fibrillated prior to operation, cerebral embolism occurred during anesthesia, whereas such occurred in only 2.8 per cent of the nonfibrillating group.

McKusick

THROMBOEMBOLIC PHENOMENA

Heppner, F.: Air Embolism Eight Hours after Ventriculography. Acta radiol. **38:** 294 (Oct.), 1952.

Eight hours after parieto-occipital ventriculography the patient died suddenly. Death was caused by air embolism. When the heart was opened under water, air bubbles were released from the right ventricle. The right auricle and ventricle were dilated.

It is postulated that air was injected into a subependymal vein which was collapsed until some mechanism increasing venous pressure occurred (such as coughing) permitting air to enter and be carried toward the heart.

Schwedel

Neuda, P. M.: Early Diagnosis and Prevention of Postoperative Thromboembolism. Am. J. Surg. **84:** 627 (Dec.), 1952.

In an attempt to elucidate the mechanisms responsible for postoperative thromboembolism, the author studied the agglomerability of the platelets, the sedimentation rate, and the plasma–red cell mass ratio of sample of blood obtained from patients before and after major surgery.

Definite changes in the various tests were noted in most of the cases by the fourth postoperative day. It was believed that in some patients these were of sufficient magnitude to favor thombosis. However, it was pointed out that the blood properties analyzed in the study were nonspecific factors which merely assisted a specific agglutinating substance and that the presence of the latter was necessary to initiate platelet agglutination.

The author also investigated the local factors in the veins of the lower extremities which exerted a potent influence on thrombus formation and on thrombus "detachability" or fitness for embolization. It was his feeling that in the horizontal position, the nutrition to the wall of the veins in the calf was impaired and hence anoxia of the intima occurred. Such a situation was conducive to venous thrombosis.

Abramson

Allen, A. W.: Management of Thromboembolic Disease in Surgical Patients. Surg., Gynec. & Obst. **96:** 107 (Jan.), 1953.

The author attempts to evaluate the various therapeutic methods utilized in thromboembolic disease associated with surgical procedures. He emphasizes the necessity of counteracting the stasis in the deep veins of the legs as a prophylactic measure and enumerates the various means to accomplish this. Early ambulation and Dicumarol are also considered advisable postoperatively. For the aged and very decrepit patient, unsuitable for the different steps used to prevent venous stasis, he proposes prophylactic superficial vein interruption.

In the presence of venous thrombosis, the author believes that quick-acting anticoagulants, like heparin and Tromexan, should be started immediately. He advocates bilateral venotomy, thrombectomy and interruption of the femoral veins if a large pulmonary embolus existed or if the patient is in the older age group. It is his belief that anticoagulants should be started 24 hours after the surgical procedure. He also calls attention to the value of procaine blocks of the lumbar sympathetics if the patient continues to have swelling and pain in the legs after the use of anticoagulants or femoral vein interruption.

Abramson

VASCULAR DISEASE

Gray, F. D. Jr., Lurie, P. R., and Whittemore, R.: Circulatory Changes in Pulmonary Arterio-venous Fistula. Yale J. Biol. & Med. **25:** 106 (Nov.), 1952.

Four cases of pulmonary arteriovenous fistula were studied by methods including cardiac catheterization and oxygen saturation determinations of arterial blood during breathing room air and 100 per cent oxygen. The only consistent clinical finding in the four patients was a characteristic x-ray picture. The expected right-to-left shunt was demonstrated in all patients, and the fraction of total blood flow thus shunted was not related to the apparent size of the tumor. In one case where it was possible to estimate the collateral flow between systemic and pulmonary arteries, evidence of a large flow through these channels was obtained. Such collateral flow tends to ameliorate the arterial anoxemia produced by the fistula. The authors also mention the possibility of additional shunting between the vascular channels of the tumor and bronchial veins.

Enselberg

Hoff, H. E.: Physiologic Problems in Peripheral Vascular Disease. Anesthesiology **13:** 628 (Nov.), 1952.

Various physiologic problems in peripheral vascular disorders are reviewed by the author. Evidence is presented supporting the concept that the sympathetic innervation of blood vessels is different in the skin as compared with the muscles of the extremities. The question of whether or not vasodilator nerves are present in man is also discussed, but no conclusions are reached. The physiologic significance of

the arteriovenous shunts and axon reflex vasodilatation are likewise touched upon.

The underlying basis for traumatic arterial spasm is not clear. Sympathectomy may have a favorable influence on this state, although this is by no means invariably so. In those instances in which no effect is produced with such a procedure, a local spasm, nonnervous in origin, can be presumed to exist.

ABRAMSON

Goodwin, J. F.: Medical Treatment of Peripheral Vascular Disease. The Pharmacological Approach. Brit. M. Bull. **8**: 371, 1952.

Rest and reflex vasodilatation are recommended methods for increasing cutaneous blood flow. The simple method of heating the *unaffected* limbs (including arms) and trunk is often forgotten. Experimental evidence as to whether dependency helps is conflicting. Priscoline appears to be the most satisfactory drug available for augmenting skin blood flow. Tolerance does not develop. The absence of generalized vasodilatation and hypotension makes it particularly desirable. There is no convincing evidence that vasodilator drugs increase muscle blood flow and ameliorate intermittent claudication. Evidence is presented suggesting that the shrinkage of the arterial tree distal to an acute arterial occlusion is due to sudden fall in blood pressure rather than spasm although the possibility of local spasm from the impact of an embolus remains. In acute occlusion total opium alkaloids and Pethidine (Demerol) are preferable to morphine because of the absence of vasoconstrictor effects. The administration of anticoagulants is imperative, but paravertebral block is unwise because of the possibility of fatal retroperitoneal hematoma. Evidence is cited, furthermore, that nervous impulses play no role in the production of spasm in large arteries.

MCKUSICK

Sharpey-Schafer, E. P.: The Peripheral Circulation in Circulatory Failure. Brit. M. Bull. **8**: 331, 1952.

Although vasoconstriction occurs in the kidney and liver, vasodilatation occurs in muscle vessels in fainting. In the presence of relatively fixed cardiac output arterial pressure may fall if there is peripheral vasodilatation as by exercise or heat. In myxedema, cardiac output is at a fixed low level. Immersion of the legs in hot water produces dilatation of previously constricted vessels with resulting sharp fall of blood pressure and unconsciousness. Marked systemic hypotension may be produced by exercise in subjects with pulmonary hypertension. The Valsalva maneuver produces syncope in the presence of vena cava obstruction and violent coughing also by a closely related mechanism. In the schoolboy fainting tricks, peripheral vasodilatation is produced by hyperventilation or squatting and fainting then produced by a modification of the Valsalva maneuver. In heart failure certain physiologic reactions of the peripheral vessels are completely reversed. In heart failure arm blood flow increases with bleeding and vasodilatation occurs with assumption of the upright posture. The afferent pathways for the production of vasoconstriction in heart failure are unknown. The most intense constriction is said to occur in acute left heart failure (gangrene of the extremities may occur in this situation), suggesting the receptors may be in the lesser circulation. Normal subjects show a decreased pulse pressure when erect; cases of heart failure show an increase. In heart failure the Valsalva maneuver produces no diminution in pulse pressure and there is no post-Valsalva drop or overshoot of pressure.

MCKUSICK

Lodin, H.: Tomographic Analysis of Arteriovenous Aneurysms in the Lung. Acta. radiol. **38**: 205 (Sept.), 1952.

A patient with arteriovenous aneurysms in the right hilar region died of meningitis secondary to the rupture of a brain abscess. Tomographic studies were performed in the postmortem specimen of the heart-lung block. These studies were further augmented by the injection of a contrast medium into the pulmonary artery.

The tomograms visualized two large aneurysms, and four smaller ones. The vessels leading to these were of uniform caliber, and from these the author draws the conclusion that a vessel proceeding towards the periphery without narrowing normally is pathognomonic of an arteriovenous fistula.

SCHWEDEL

Hunter, W. C., and Lium, J. H.: Unusual Pathologic Manifestations of Dissecting Aortic Aneurysm. Am. J. Path. **28**: 1035 (Nov.), 1952.

The authors present four unusual cases of dissecting aneurysm. The first case was that of a double barreled dissection in which old communication between the two channels was found high at the upper thoracic level of the aorta, the distant end of the false tube ending blindly almost at the level of the bifurcation. The second case was unique in that during the deep dissection into the root of the aorta, the right coronary artery for a short distance was separated from the adjacent aortic structure and set adrift in the space created by the dissection. With healing, the isolated vessel traversed this space to regain the outer wall of the aorta, but in doing so was flattened (but patent) which was the likely basis for the coronary insufficiency in this case. Nearby three small fenestrations in the "partition" wall permitted communication between the two barrels of this old dissecting aneurysm. The authors speculate on the possible role of these fenestrations in the development of the aortic murmurs and the associated blood pressure record of 180/0.

The third case was marked by multiple dissections with matching clinical phenomena.

The fourth case was featured by incomplete development, remaining as a striking intramural cleft traceable to the lumen of the aorta but not progressing to the adventitia. No hematoma was present; it presumably had been absorbed.

All of these cases show interesting clinicopathological aspects.

GOULEY

Morrison, L. M.: Diet and Atherosclerosis. Ann. Int. Med. **37:** 1172 (Dec.), 1952.

Statistical studies seem to indicate that the lowered mortality rate from coronary artery disease in various European countries during World War II was due to the lowered intake of fat and cholesterol in such population groups. For this reason, the dietary approach in the management of patients with atherosclerosis is stressed, the low cholesterol, low fat diet being particularly directed to those in whom examination of the blood reveals an abnormal cholesterol-phospholipid ratio. In addition, lipotropic agents and thyroid extract may prove beneficial in certain selected cases.

WENDKOS

Jackson, R. S., and Wilkinson, C. F., Jr.: The Ratio Between Phospholipid and the Cholesterols in Plasma as an Index of Human Atherosclerosis. Ann. Int. Med. **37:** 1162 (Dec.), 1952.

The phospholipid–total cholesterol ratio is an inherently unsound index for establishing the presence of abnormal lipoid metabolism since one of its components—total cholesterol—exists only in the imagination of the chemist. Under conditions where the free cholesterol forms a constant proportion of the total cholesterol, a mathematical relationship can be demonstrated between phospholipid and total cholesterol, but this is a mathematical device and not a biologic relationship. Diseases which are the end result of atherosclerosis or which predispose to this vascular lesion can be shown to have lower average phospholipid-free cholesterol and phospholipid-total cholesterol ratios than normal individuals, but they do not differ significantly in this respect from values predicted from a large miscellaneous group. Similar reductions in this ratio can be observed in individuals with essential familial hypercholesteremia who are genetically heterozygous abnormal, and who could not be shown to be especially prone to atherosclerosis. Finally, the decreased phospholipid–total cholesterol ratios observed in certain disease states simply reflect a higher average circulating cholesterol level, and possess no other significance.

WENDKOS

Rose, L. B.: Obstruction of the Superior Vena Cava of Twenty-five Years' Duration. J.A.M.A. **150:** 1198 (Nov. 22), 1953.

This case has been presented because of several points of interest. (1) There was a gradual onset of signs and symptoms during and after a period of recurrent severe infections of the chest wall, strongly suggesting thrombophlebitis as a cause. (2) Involvement of the azygos vein was proven by angiograms and clinical tests. (3) There is a prolonged survival time (25 years) indicating adequate compensatory collateral circulation. At the time of writing the patient is living and well with minimal symptoms after 25 years.

KITCHELL

Malinow, M. R., Hojman, D., and Pellegrino, A. A.: Experimental Production of Localized Atheromatous Lesions in the Rat. Rev. argent. cardiol. **19:** 165, 1952.

Atheromatous-like lesions were locally induced in rats by injecting cholesterol buffered solutions into doubly ligated femoral arteries. It is thus demonstrated that the arteries of the rat are able to show an "atheromatous response" when appropriate stimuli are used. It is furthermore pointed out, that this preparation is especially suited to study the local metabolization of cholesterol by the arterial wall under different circumstances.

AUTHORS

Gilroy, J. C., Marchand, P., and Wilson, V. H.: The Role of the Bronchial Veins in Mitral Stenosis. Lancet **2:** 9597 (Nov. 15), 1952.

The authors describe two systems of bronchial veins:

1. The true bronchial veins, which accompany the bronchi as far as the respiratory bronchioles, are tributaries of the pulmonary veins. The corresponding arteries are derived from the aortic system.

2. The "pleurohilar" vessels supply and drain the hilar structures and the subpleural plane. The "pleurohilar" arteries are likewise aortic in origin but the corresponding veins empty via the azygos, hemiazygos and intercostal veins into the right side of the heart. The "pleurohilar" veins also communicate freely with the pulmonary venous system. At necropsy in six cases and at operation in 30 cases striking engorgement of the pleurohilar veins was seen. Although dilatation of the true bronchial veins is probably responsible for hemoptysis in mitral stenosis, dilatation of the "pleurohilar" veins may result in a sizeable left-to-right shunt which contributes significantly to the burden on the right heart.

MCKUSICK

Grafflin, A. L., and Bagley, E. H.: Studies of Peripheral Blood Vascular Beds. Bull. Johns Hopkins Hosp. **92:** 47 (Jan.), 1953.

A study of peripheral blood vascular beds was performed upon frogs using the compound microscope. The skin, web, ventral surface of the tongue and urinary bladder were examined. A similar type of investigation was carried out on the bulbar con-

junctiva of rabbit and man, and on the finger, nail bed, skin, and mucosa of lower lip of the latter. The most consistent finding was the presence of irregularly dichotomous capillary beds, with a variable number of arteriovenous communications. The authors were unable to confirm the existence in the various beds studied of structural and functional units built around a preferential, capillary-like, "thoroughfare" channel.

ABRAMSON

Tobin, C. E.: The Bronchial Arteries and their Connections with Other Vessels in the Human Lung. Surg., Gynec. & Obst. **95:** 741 (Dec.), 1952.

A study was performed to obtain further information on the embryologic origin of the bronchial arteries, on their course and anastomoses with the pulmonary artery, and on their relationship to the other pulmonary vessels in normal and pathologic lungs. For part of the investigation, human embryos were used, isolated lungs from uninjected and injected specimens being studied. Similar procedures were carried out on the lungs of patients varying in age from a few days to 91 years.

In the case of the embryos, it was found that the blood supply to the developing lungs at first consisted of a series of small segmentally arranged branches from the dorsal aortas and that later some of the cranial blood vessels atrophied while others were formed further caudad. Eventually definitive branches developed which became the main arteries.

In the lung of the child and adult, anastomoses were frequently found between bronchial and pulmonary arteries. These were either short (1 to 2 mm.) or long (10 to 40 mm). Shunts larger than capillaries were also noted between the branches of the pulmonary artery and the pulmonary veins. It was believed that these had the function of shunting blood away from a part not requiring a large circulation or reducing elevated local pressures.

It was concluded that the circulation to the lungs was not as simple as some of the current concepts might indicate.

ABRAMSON

Wilkinson, W. R.: Abdominal Aortic Aneurysm; Report of a Case Treated with Reactive Cellophane. Surg., Gynec. & Obst. **96:** 82 (Jan.), 1953.

A case of abdominal aneurysm treated with reactive cellophane is reported. The lesion was fusiform in type and extended from the level of the duodenum to the bifurcation of the aorta. Since there were two small, thinned out areas on the anterior surface of the aneurysm, it was decided to cover the mass with several layers of reactive cellophane. Before this was done, all structures in contact with the aneurysm were mobilized and separated from it so that they would not come in contact with the irritating material. The postoperative course was complicated by a high fever, partial intestinal obstruction, and swelling of both legs. The patient died about 15 months after surgery from a rupture of the same aneurysm into the duodenum.

ABRAMSON

OTHER SUBJECTS

Ask-Upmark, E.: Cardiac Involvement in Neoplastic Conditions. Cardiologia **21:** 506 (Fasc. 4/5), 1952.

Neoplastic alterations of the heart may cause disturbances of cardiac activity and imitate other cardiac affections. This may be due to tumors in the neighbourhood of the heart including tumors of certain nervous structures or endocrine organs and thoracic arteriovenous aneurysms, or to tumors of the heart. Various neoplasms of the latter group are described and a case of myxoma of the left auricle observed by the authors is reported. As usual, this case was diagnosed only post mortem but several possible diagnostic features are pointed out. An intra-auricular myxoma may be suspected in the presence of signs of mitral stenosis without rheumatic history, with variable ausculatory findings especially after change of position of the patient. Additional signs may be prolonged fever in the absence of subacute bacterial endocarditis, attacks of syncope and/or ischemia involving simultaneously all four extremities. The recognition of such a tumor during lifetime has become of practical interest in view of the possibility of its surgical removal.

PICK

Dawes, G. H.: Reflexes from the Heart and Lungs. Brit. M. Bull. **8:** 324, 1952.

This is a review of current knowledge of reflexes which, originating from receptors in the heart and lungs and mediated by afferent fibers in the vagi, cause alterations in the circulation and in the movements of respiration. The author points out the conflict in evidence relative to Bainbridge's experimental observations. In the vagus of the cat the afferent "venous-pressure fibers," presumably from the right auricle and great veins, are almost as numerous as the depressor fibers, yet their role in maintenance of the circulation is not fully understood. Venous pressure fibers show two bursts of impulses, one just after the P wave and the other just after the T wave of the electrocardiogram. Bezold in 1867 demonstrated that the fall in blood pressure, heart rate, and rate of respiration from intravenous injection of veratrum alkaloids was abolished by section of the vagi. Jarisch and his colleagues consider that most of the afferent impulses responsible for veratrine depression come from the ventricular myocardium and that the physiologic counterpart of the Bezold reflexes lies in myocardial stretch receptors stimulated by a rise in left ventricular pressure. The Hering-Breuer re-

flex is briefly reviewed. Reflex phenomena excited by changes in the pulmonary circulation are reviewed with the evidence for receptors on both the arterial and the venous side of the lesser circulation. The reflex production of rapid shallow respiration by experimentally produced multiple minute pulmonary emboli (Shaw, 1919) is of great interest. Various injected chemicals, particularly amidine derivatives, likewise stimulate pulmonary vascular receptors. Aortic stretch and chemoreceptors are discussed briefly. The author emphasizes the complexity of reflex mechanisms in the heart and lungs.

McKusick

Briscoe, W. A.: Further Studies on the Intrapulmonary Mixing of Helium in Normal and Emphysematous Subjects. Clin. Sc. **2**: 45 (Feb.), 1952.

The author described a method for assessing ventilation and the volume of the poorly ventilated space in the lungs, and used it in studying the mixing of helium in model lungs and in the lungs of elderly normal and emphysematous subjects. The procedure consisted of a spirometer to which was added a quick acting katharometer.

In only a few of the normal subjects was there any detectable inequality in ventilation of the lungs, and in none did the poorly ventilated space exceed 1 liter. On the other hand, almost all the emphysematous patients had more than 1 liter of poorly ventilated space, and this usually received less than a fifth of its share of the ventilation of the whole lung.

Abramson

Bates, D. V.: The Uptake of Carbon Monoxide in Health and in Emphysema. Clin. Sc. **2**: 21, 1952.

Using a respiratory method of estimating the rate of uptake of carbon monoxide, the author compared the results in normal subjects with those obtained in a series of patients suffering from emphysema.

It was found that the percentage uptake of carbon monoxide in emphysema was considerably lowered, being 29 per cent of inspired gas, as compared with 53 per cent for a young normal group and 47 per cent for an old normal group. The findings in the emphysematous patients were considered to indicate that much of the inspired air was not coming in contact with pulmonary blood.

Abramson

Taylor, H. L., Brozek, J., and Keys, A.: Basal Cardiac Function and Body Composition with Special Reference to Obesity. J. Clin. Investigation **31**: 976 (Nov.), 1952.

It has been reasoned that in the presence of obesity cardiac output and cardiac work in the basal state are increased approximately in proportion to the increase in oxygen consumption. In reinvestigating this problem, the authors determined the basal cardiac outputs of 34 healthy male students by the acetylene technic. The amount of body fat was calculated from the specific gravity of the body, determined by the water immersion method. The basal cardiac output was related to body weight by a correlation coefficient of 0.54, to surface area by a coefficient of 0.60, and to weight of the lean body mass by a coefficient of 0.74. No relationship was found between blood pressure measured intra-arterially and body size or composition. The arteriovenous oxygen difference was positively correlated with fat and negatively correlated with lean body mass. Since the cardiac output is equal to the oxygen consumption divided by the arteriovenous difference, it follows that the basal cardiac output is not strictly proportional to surface area and to oxygen consumption in individuals with different body compositions. Persons with a relatively small lean body mass and a relatively large mass of fat will have cardiac outputs which are definitely less than that predicted from surface area or oxygen consumption. These conclusions apply only to healthy young men in the twenties and do not necessarily apply to other age groups.

Waife

Mills, C. W.: Simple Clinical Aid in Diagnosis of Hemorrhagic Pericardiac Effusion. J.A.M.A. **150**: 1208 (Nov. 22), 1953.

The author reports a case wherein the injection of 10 per cent calcium gluconate solution through an exploratory pericardicentesis needle was helpful in determining the source of gross blood obtained initially through the aspiration needle. The patient was familiarized with the end point sensation of a calcium gluconate circulation time determination prior to the injection of this substance through the pericardicentesis needle. Rationale of the procedure and the possibilities of misleading results are discussed. It is recommended that each initial pericardicentesis be preceded by circulation time determination so that advantage may be taken of the above described technic if the situation necessitates clarification.

Kitchell

Wood, P.: Pulmonary Hypertension. Brit. M. Bull. **8**: 348, 1952.

Factors influencing pulmonary artery pressure are discussed as follows: pulmonary vascular bed, pulmonary blood flow, alveolar oxygen tension, left auricular pressure, drugs. Peripheral pulmonary vascular resistance calculated from Poiseuille's equation may be expressed in empiric units or as dynes per second per centimeter^{-5}. Six clinical types of pulmonary hypertension are discussed: embolic, primary (idiopathic), specific arteritis, pulmonary plethora (septal defects, patent ductus arteriosus), mitral stenosis, chronic cor pulmonale. The clinical features of each type is described in detail. The giant *a* wave of the venous pulse (which may

have an expression in a presystolic pulsation of the liver) is emphasized as a conspicuous feature of many cases. From the author's experience pulmonary plethora, per se, does not appear to be a consistent cause of pulmonary hypertension; in fact pulmonary vascular resistance is usually diminished. Of 50 cases of auricular septal defect only six showed elevated mean arterial pressures and pulmonary resistance values. Since the average age of these six patients was less than that of the whole group (the youngest of the six was 2½ years old) a congenital rather than acquired basis is postulated. In an unselected series of 25 acyanotic cases of ventricular septal defect only five showed elevation of pulmonary artery pressure and vascular resistance. In a consecutive series of 40 acyanotic cases of patent ductus arteriosus, three had moderate pulmonary hypertension which the author terms benign, that is, due merely to torrential pulmonary blood flow with no increase in pulmonary vascular resistance. Ten had severe pulmonary hypertension with very high resistance values. The average age was again lower than that of the entire group, making it difficult to hold the duration of the shunt responsible for the increased vascular resistance. Clinical signs assist in distinguishing this last group. In the mitral stenosis group the development of high peripheral vascular resistance ("protective pulmonary hypertension") produces a change in the clinical picture and physical findings. The author has not witnessed a case of protective pulmonary hypertension which proved irreversible after technically successful valvulotomy. Obliteration of the pulmonary capillaries, reduced alveolar oxygen tension, and increased pulmonary blood flow, all play roles in the pulmonary hypertension of cor pulmonale. However, in the experience of the author pulmonary hypertension adequate to produce congestive heart failure is relatively rare in emphysema. When heart failure does occur it is usually the result of pulmonary artery pressure elevation from attacks of bronchitis or bronchopneumonia. A proposal for the surgical treatment of primary pulmonary hypertension is made: anastomosis of the pulmonary arterial tree with the *distal* end of a subclavian artery.

McKusick

Schilero, A., Antzis, E., and Dunn, J.: Friedreich's Ataxia and its Cardiac Manifestations. Am. Heart J. **44:** 805 (Dec.), 1952.

The cardiac findings in eleven patients (eight men and three women) with Friedreich's ataxia are presented. Eight patients had no cardiac symptoms. Two cases evidenced congestive failure; one of these also had paroxysmal auricular tachycardia; a third patient had paroxysmal auricular fibrillation. The heart was enlarged in three patients; in two it was associated with congestive heart failure. Murmurs were found in three patients; one had presystolic and early systolic apical murmurs, the other two had systolic murmurs over the aortic and pulmonic areas and the left second intercostal space, respectively. There were two deaths in this series of 11 patients, one of bronchopneumonia and one of congestive heart failure. The electrocardiographic changes included inverted or iso-electric T waves in the standard limb leads and inverted T waves in the precordial V leads.

The pathologic findings in the one patient in this series who died (age 29 years) included (1) cardiac hypertrophy, (2) diffuse interstitial fibrosis of the myocardium, (3) fatty degeneration of the myocardium, and (4) round cell infiltration with lymphocytes and eosinophils.

The authors state that the cardiac symptoms, signs and pathologic findings in their series bear out the results found in other reports.

Rinzler

Leichtling, M., Reibstein, H. B., Stein, M. H., and Bass, H. E.: Carcinoma Diagnosed by Examination of Pericardial Fluid. New England J. Med. **247:** 884 (Dec. 4), 1952.

Antemortem diagnosis of malignant pericardial effusion is said to be made infrequently. The cases of a man aged sixty-two years and a woman aged fifty-two years are reported. A hemorrhagic pericardial effusion containing neoplastic cells was present in each of them. In one patient supraclavicular lymph nodes were found to be involved by an anaplastic carcinoma, possibly from stratified squamous epithelium. In the second case a primary bronchogenic carcinoma was ultimately found. In this case the carcinomatous cells in the pericardial fluid were the first sign of the bronchogenic carcinoma. It is emphasized that the suspicion of cancer should be aroused in the presence of hemorrhagic pericardial effusion in elderly patients.

Rosenbaum

Murphy, R. V., Coffman, E. W., Pringle, B. H., and Iseri, L. T.: Studies of Sodium and Potassium Metabolism in Salt-Losing Nephritis. Arch. Int. Med. **90:** 750 (Dec.), 1952.

In the present case, a 30-year old patient with salt-losing, but potassium-retaining, nephritis was studied for a total period of 24 months. Treatment of uremia during the initial hospitalization with large quantities of dextrose and smaller quantities of saline infusions lowered the blood nonprotein nitrogen, but at the same time produced an alarming episode of hypopotassemia and hyponatremia with generalized muscular weakness and respiratory paralysis. The response to potassium chloride salts was dramatic. It was found subsequently that 18 Gm. of sodium chloride and 5 Gm. of sodium bicarbonate were necessary to maintain hydration and sodium balance. In addition, metabolic balance studies, including urine and stool analyses, indicated an optimal intake of potassium somewhere between

1 Gm. (25 mEq.) and 2 Gm. (50 mEq.) a day. Restriction of potassium to 1.5 Gm. (37.5 mEq.) a day was successful in keeping the plasma potassium concentrations near normal levels. Failure of a therapeutic trial with desoxycorticosterone and an adequate eosinophilic response in adrenocorticotropic hormone ruled out the possibility of adrenal cortex insufficiency. The literature is reviewed for the purpose of elucidating the etiologic, pathologic, and clinical aspects of this syndrome.

BERNSTEIN

Evans, W.: Oesophageal Contraction and Cardiac Pain. Lancet **2:** 1091 (Dec. 6), 1952.

In 332 patients with "cardiac-like pain" but normal electrocardiograms the author found barium-fluoroscopic evidence of abnormality of eosophageal contraction ("eosophageal arrhythmia") in 133 (40 per cent). In a group of 200 healthy subjects under 45 years of age, 500 healthy subjects over 45, 500 cases of myocardial infarction, and 200 cases of heart disease without pain, esophageal arrhythmia was seen in only 2.6 per cent. The first phase of esophageal arrhythmia is characterized by spasm affecting the lower third of the gullet, the second phase by a sharp recoil of the barium up the gullet. Reassurance and sedation provided the most consistent benefit. Discontinuance of smoking, belladonna and carminatives also helped.

McKUSICK

Shearn, M. A., and Pirofsky, B.: Disseminated Lupus Erythematosus. Arch. Int. Med. **90:** 790 (Dec.), 1952.

Thirty-four cases of disseminated lupus erythematosus are analyzed from the standpoint of clinical and laboratory features and response to therapy. Every case was confirmed by demonstration of the L. E. cell, pathologic material, or both. The age of onset varied from 3 to 56 years; 19 of the patients were over 30. Of the 31 women, 8 were outside the child-bearing age.

The symptomatology was varied and often bizarre. All patients had fever, and 31 had skin lesions. A nephrotic state was present in four patients. Chronic nonsuppurative parotitis was noted in three patients. Six patients had a history of a preceding skin eruption which was believed to be chronic discoid lupus erythematosus. Cardiac symptoms were found to be prominent. Congestive failure occurred in 8 and hypertension in 11. Systolic murmurs were common. Two patients with diastolic apical murmurs were found at necropsy to have had Libman-Sacks endocarditis. The electrocardiogram was considered abnormal for 21 of 29 patients. The sedimentation rate was elevated in all patients, and all but one had anemia. Other abnormal laboratory findings included leukopenia in 74 per cent, and abnormal albumin-globulin ratio in 69 per cent, proteinuria in 62 per cent, hematuria in 35 per cent, and a positive Wasserman reaction in 19 per cent. Three patients clinically suspected of hemolytic anemia had a positive Coombs test.

L.E. cells were found in 29 of the 31 patients who were tested, an incidence of 94 per cent. When the patients were acutely ill, L.E. cells were regularly demonstrable. With improvement or remission, the cells usually decreased in number and occasionally disappeared from the blood and marrow. Twenty of the patients received corticotropin (ACTH) or cortisone. The results were encouraging in the majority. However, four patients died while receiving the hormones; two patients who responded initially later became refractory to the treatment and died. Case histories are presented in order to illustrate some of the features of disseminated lupus erythematosus. Because systemic manifestations so frequently precede the rash (in 41 per cent), the importance of high index of suspicion is stressed.

BERNSTEIN

Posteli, T., Garbini, G. C., and Morelli, L.: The Arteriolar Pulsations of the Organs of the Splanchnic Area Studied by means of Photoplethysmography. 4th Inter-American Congress of Cardiology. Rev. argent. cardiol. **19:** 363, 1952.

The authors have recorded the arteriolar pulsations of splanchnic organs (kidney, pancreas, gut, liver) of the dog by an original application of photoplethysmography. The patterns of these micropulsations are described in basic conditions and in various conditions. Response to adrenergic agents, myocardial extracts, or to reflex stimulation (stretching of the mesentery, pulling on the viscera, gastric insufflation) are studied. The authors state that the visceral vasomotor response does not differ from the response usually observed in the peripheral areas.

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APPLICATIONS FOR GRANTS-IN-AID

Applications for research grants-in-aid for the Association's 1954–55 fiscal year must be filed by Dec. 1, 1953. Information and application forms may be obtained from the Medical Director.

SCIENTIFIC PROGRAM OF SECTION ON CLINICAL CARDIOLOGY

The Section on Clinical Cardiology of the American Heart Association will sponsor a two-day scientific program at the Conrad Hilton Hotel in Chicago on April 3 and 4, 1954. This program will follow the Annual Meeting of the Assembly of the American Heart Association and will immediately precede the Annual Sessions of the American College of Physicians. The meeting will be open to all members of the medical profession. Wright R. Adams, M.D., Chicago, is Chairman of the Program Committee. Any member of the American Heart Association who wishes to present a paper should send a 250 to 300 word abstract of the proposed paper to Charles D. Marple, M.D., Medical Director, American Heart Association, 44 East 23rd Street, New York 10, N. Y. All papers should be on subjects of distinct clinical interest. *The deadline for the receipt of abstracts is Jan. 1, 1954.*

VOCATIONAL COUNSELING STUDY

A pilot study in the field of vocational counseling for school children with heart disease has been launched in New York City under the joint auspices of the American and New York Heart Associations. The study will be conducted by the Vocational Advisory Service of New York over a seven-year period and will provide guidance in the choice of their future occupations to 360 eighth and ninth grade children. The objective is to help them avoid unsuitable jobs and the possible physical damage which may result in premature unemployability, and also to assemble data which would furnish a basis for community programs in this field in all parts of the country. Among the questions to which the study will seek an answer are the extent to which existing vocational counseling facilities serve young cardiacs and the special problems they face in relation to job training and subsequent employment.

AID TO PARENTS OF RHEUMATIC FEVER PATIENTS

To guide parents in making a long period of bed rest more endurable for children with rheumatic fever, the Association has issued a new pamphlet, *Have Fun . . . Get Well.* J. G. Fred Hiss, M.D., Chairman of the Association's Council on Rheumatic Fever and Congenital Heart Disease, explains in a foreword that the purpose of the booklet is "to help patients make this time of physical repair a period that is also mentally and spiritually constructive." The first section of the pamphlet, addressed to teenagers, was written by Maryelle Dodds, OTR, and is based on data she gathered while working with rheumatic fever patients at Los Angeles County General Hospital. The second section, for younger children, and an extensive bibliography were prepared by the American Heart Association. Now available from affiliated Heart Associations, the booklet is recommended for physicians to give to parents of rheumatic fever patients.

NEW CHAIRS OF CARDIOVASCULAR RESEARCH

A Chair of Cardiovascular Research is being established at both the Medical College of Georgia, at Augusta, and at Emory University School of Medicine, Atlanta, following a decision by the Georgia Heart Association to grant $12,000 to each school for this purpose. The agreements leading to this new form of research support also provide that each school will

establish a laboratory to be known as the "Georgia Heart Association Laboratory of Cardiovascular Research."

NEW ENGLAND CARDIOVASCULAR SOCIETY

The New England Cardiovascular Society has planned a series of five meetings as part of its scientific 1953–54 program. They will be held at the Morse Auditorium, Museum of Science, Science Park, Boston, at 8:00 p.m., on the following dates: November 2, January 4, February 8, March 8 and May 10. Papers are invited from members in New England for the January 4 meeting. Titles should be sent as soon as possible to the President, Edward F. Bland, M.D., Massachusetts General Hospital, Boston. Interested physicians, medical students and members of the New England Postgraduate Assembly are invited to attend all sessions.

PILOT STUDY IN POSTGRADUATE MEDICAL EDUCATION

The New Hampshire Heart Association, in cooperation with the American Heart Association, has launched a pilot project in postgraduate medical education in the hope of determining which are the best methods for informing the general practitioner in less-populated areas about the present state of knowledge in the cardiovascular field. Teams of medical experts are visiting four centers in the state for intensive sessions with local physicians in each area. In the course of these practical but informal sessions, various types of teaching methods—lecture, panel discussions, films and other visual aids—are being utilized. Evaluation procedures are being planned in an effort to ascertain later which method proved most effective in conveying the new material to the physician.

Physicians who spoke at the opening sessions during October included E. Cowles Andrus, M.D., President-Elect of the American Heart Association and Associate Professor of Medicine at Johns Hopkins University, Baltimore; Joseph B. Vander Veer, M.D., Assistant Clinical Professor of Medicine, University of Pennsylvania, Philadelphia and Reno R. Porter, M.D., Associate Professor of Medicine and Director of the Cardiovascular Laboratory, Medical College of Virginia, Richmond, Va. The general topic of the first series was congestive heart failure, with emphasis on methods of therapy. One-day sessions were held from October 19 through October 22 at Manchester, Rochester, Laconia and Hanover.

The November series of one-day sessions is scheduled for Manchester on the 16th, Rochester on the 17th, Laconia on the 18th and Hanover on the 19th. The topic will be rheumatic fever. Additional sessions are being planned for April and May of next year. Depending on the success of the New Hampshire sessions, similar programs may be held in other parts of the nation.

MEETINGS

Nov. 9–13: American Public Health Association; Hotel Statler, New York. Reginald M. Atwater, M.D., Executive Secretary, 1790 Broadway, New York 19.

Nov. 9–13: American School Health Association; Hotel New Yorker, New York. A. O. DeWeese, M.D., Secretary, 515 E. Main St., Kent, Ohio.

Nov. 20: "Heart-in-Industry" Conference, New York Heart Association; Hotel Statler, N. Y. Norman Plummer, M.D., Chairman of Steering Committee, New York Heart Association, 270 Park Avenue, New York 17.

Dec. 1–4: American Medical Association, Seventh Annual Clinical Session; Jefferson Hotel and Kiel Auditorium, St. Louis, Mo.

Jan. 4: American Federation for Clinical Research, Eastern Section, Jimmy Fund Building, Children's Medical Center, Boston. Jan. 28: Western Section, University of Oregon Medical School, Portland. Jan. 29: Southern Section, Jung Hotel, New Orleans.

March 27–28: American Psychosomatic Society, Eleventh Annual Meeting; Jung Hotel, New Orleans. Titles and abstracts of papers in quadruplicate by Dec. 1 to George L. Engel, M.D., Chairman, Program Committee, 551 Madison Avenue, New York 22.

April 1–4: Thirtieth Annual Meeting, American Heart Association; Conrad Hilton Hotel, Chicago.

April 1–2: Assembly of the American Heart Association.

April 3–4: Scientific Sessions of Section on Clinical Cardiology of the Scientific Council, American Heart Association.

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*Beckman, H.: Pharmacology in Clinical Practice. Philadelphia, W. B. Saunders Company, 1952, p. 172.

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